Management of Comorbid Bipolar Disorder and Substance Abuse

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Bipolar disorder is a severe and often chronic disorder with lifetime prevalence rates of bipolar spectrum disorders of up to 6.5% in the general population. Patients with bipolar disorder frequently report co-occurring substance use disorders, and the rates of alcohol and other substance use disorders are significantly higher in persons with bipolar disorder than in the general population. The present review discusses why people with bipolar disorder use substances, provides an overview of the impact of alcohol and other substance use on the course of bipolar disorder, and outlines the treatment options currently available to patients with co-occurring bipolar disorder and substance abuse. Our aim is to summarize the existing data on the pharmacologic treatment options and to include the most recent published data whenever possible. Three randomized, placebo-controlled studies of dual-diagnosis patients treated with carbamazepine, lithium, and valproate are discussed. The results are generally positive and support the use of these agents in dual-diagnosis patients. Open-label studies are also presented, and the need for controlled data is outlined. The review also briefly discusses the psychotherapeutic approaches to patients with comorbid bipolar and substance use disorders.

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Bipolar disorder is a severe, recurrent, and often chronic psychiatric illness that is characterized by periods of depression interposed with episodes of mania or hypomania and with mixed episodes. Until recently, clinical attention concentrated primarily on bipolar I disorder, in which patients experience at least 1 episode of mania and depression in the course of their illness. The prevalence of bipolar I disorder ranges from 0.8% to 1.7% in epidemiologic studies.[1–3] In the Epidemiologic Catchment Area (ECA) study of 20,291 respondents, the estimated U.S. population lifetime prevalence of bipolar I and II disorders was 1.3%.[4] In the National Comorbidity Survey, the lifetime prevalence of mania was 1.6%.[2] However, it is increasingly recognized that bipolar disorder encompasses a much broader spectrum of illnesses than bipolar I disorder and includes bipolar I and II disorders, bipolar disorder not otherwise specified (NOS), cyclothymic disorder, and other forms of bipolar illness. Recent literature suggests that these forms of bipolar disorder are more prevalent in community samples than bipolar I disorder.[5,6] The lifetime rate of bipolar spectrum disorder is estimated to be between 3% and 6.5%.[1]

Alcohol and other substance abuse and dependence are also common. The estimated U.S. population lifetime prevalence of any substance use disorder is between 9% and 17%.[4,7] In the ECA study, the estimated U.S. population lifetime prevalence of alcohol abuse or dependence was 13.5%, and the lifetime prevalence of other drug abuse or dependence was 6.1%.[4] In the National Comorbidity Survey of 8098 respondents, the lifetime prevalence of any substance use disorder was 26.6%.[8] The lifetime prevalence of alcohol abuse was 9.4% and of alcohol dependence 14.1%; the lifetime prevalences of drug abuse and dependence were 4.4% and 7.5%, respectively.[2]

COMORBIDITY OF BIPOLAR DISORDER AND SUBSTANCE ABUSE

The prevalence rates of substance use disorders in patients with bipolar disorder are much higher than in the general population. In the United States, 3 large population-based studies have examined the prevalence rates of comorbid substance abuse and bipolar disorder.[4,7,8] All 3 studies have shown that the rates of substance use disorders are considerably higher in bipolar patients than in the general population. In the ECA study, 61% of patients with bipolar I disorder and 48% of patients with bipolar II disorder had comorbid substance abuse or dependence.[4] The reported lifetime prevalence of any alcohol

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diagnosis in patients with a bipolar diagnosis (bipolar I or II) was 44%, and the lifetime prevalence of drug abuse and/or dependence was 34%.[4] Bipolar disorder had a higher lifetime prevalence of comorbid substance use disorders than other major psychiatric disorders such as schizophrenia (47%), unipolar major depression (27%), and anxiety disorders (24%).[4] Consistent with the results of the ECA study, in the National Comorbidity Survey, both men and women with a lifetime diagnosis of alcohol dependence had significantly higher odds of having a co-occurring diagnosis of mania than persons without alcohol abuse or dependence.[8,9] The lifetime odds ratios in patients with a history of mania were 0.3 for alcohol abuse, 9.7 for alcohol dependence, 1.2 for drug abuse, and 8.4 for drug dependence.[8,9] The relatively low odds of lifetime co-occurrence of substance abuse and bipolar disorder and the high odds of dependence seem to demonstrate that when people with bipolar disorder have a substance-related disorder it tends to be severe and consistent with dependence rather than abuse.

The most recent survey, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC),[7] assessed the comorbidity of substance use disorders with 9 mood and anxiety disorders in a nationally representative U.S. sample of 43,093 respondents. The 12-month prevalence of mania and hypomania among all respondents was comparable to the results reported by previous surveys (1.7% for mania and 1.2% for hypomania). In persons with a 12-month history of substance use disorders, the prevalence of mania increased to 5% and the prevalence of hypomania increased to 3.4%. Additionally, the rates of substance use disorders were significantly higher in persons with a history of mania or hypomania than in persons without a mood disorder. The 12-month prevalence of substance use disorders was 27.9% in persons with a history of mania and 26.6% in those with a history of hypomania (while the rate of substance use disorders was 9.4% in persons without a mood disorder).[7]

WHY DO PEOPLE WITH BIPOLAR DISORDER USE SUBSTANCES?

The reasons for the high rates of substance use in bipolar disorder are not well understood.[10,11] Possible explanations include overlapping symptoms and resulting mood disorder misdiagnosis, self-medication of mood symptoms, substance abuse causing the development of bipolar disorder, and a common genetic vulnerability.[10,11] None of these models explain all of the data.[11] It has also been hypothesized that impulsivity, which features prominently in both bipolar disorder and substance use disorders, may contribute to the overlap between the disorders.[12,13] While it is unclear whether greater impulsivity in individuals with bipolar disorder predisposes them to substance use disorders, or impulsivity associated with substance use disorders precedes bipolar disorder, it has been shown that patients suffering from both bipolar disorder and substance use disorders show higher impulsivity than individuals with bipolar disorder or substance use disorders alone.[13]

The role of mood state as a risk factor for drug abuse has been the topic of little research. Estroff et al.[14] reported a trend ($p = .072$) toward greater abuse of drugs during manic rather than depressive episodes in a small ($N = 36$) sample. Several studies have reported substantially higher rates of drug use in patients with rapid-cycling or mixed (dysphoric) mania than with "pure" or "euphoric" mania,[15–18] but 1 study[19] reported contrary findings. Whatever the etiology, substance use in patients with bipolar disorder does not appear to be a temporary and purely mood-dependent condition.[11]

IMPACT OF SUBSTANCE ABUSE ON THE COURSE OF BIPOLAR DISORDER

The negative impact of substance use disorders on bipolar disorder is well documented. A survey of 500 U.K. and U.S. psychiatrists assessed the barriers, challenges, and unmet needs that the psychiatrists were facing in the recognition, diagnosis, and management of patients with bipolar disorder.[20] They found that bipolar patients with the highest level of unmet needs were those with comorbid alcohol and other substance use disorders, followed by those with a rapid-cycling bipolar pattern. Psychiatrists from the United States identified poor treatment adherence as the main barrier in treating bipolar patients with comorbid substance use disorders. They also felt that difficulties in diagnosis and the need for abstinence and stabilization before bipolar disorder can be treated contributed to the challenge of treating this subpopulation of bipolar patients. Psychiatrists in the United Kingdom identified service provision issues, difficulties in diagnosis, and poor adherence as the main unmet needs of patients with comorbid bipolar disorder and substance use disorders.[20]

Increased treatment nonadherence in bipolar patients with comorbid substance use disorders compared to bipolar patients without substance use disorders has been documented in a number of studies.[10,21,22] Medication nonadherence has been implicated in delayed symptomatic and functional recovery in patients with bipolar disorder[23,24] and was proposed as the cause of higher rates of relapse in bipolar patients.[25] It has been found that substance use disorder is one of the major causes of treatment nonadherence in bipolar individuals.[22] A recent study in veterans with bipolar disorder investigated a variety of factors (such as symptoms, overall health status, functional level, gender, and substance use disorder) and found that only substance use disorder was associated with treatment nonadherence.[22] Past substance abuse was not associated with treatment nonadherence. The finding points to the fact that

immediate issues associated with substance use disorders (such as intoxication, poor judgment, and impulsivity) affect treatment adherence and that addressing substance use disorders in bipolar patients would be beneficial from the treatment-adherence and, consequently, symptomatic-improvement perspective.[22]

Comorbid alcohol and drug use disorders negatively affect the course and treatment outcome of bipolar disorder. Recovery from bipolar disorder is less likely in patients with past or current comorbid substance use disorders than in patients without substance use disorders; recovery is less likely in patients with current than with past substance use disorders.[26] Patients with current or past substance use disorders report lower quality of life than patients with bipolar disorder and no substance use disorders.[26,27] Increased rates of hospitalization[17,24,28–30] and lower rates of recovery during hospitalization are also reported in bipolar patients with substance use disorders.[31] In addition, aggression and violence were significantly greater in bipolar patients with comorbid substance abuse.[32,33] Patients with bipolar disorder and comorbid substance use disorders have a significantly increased lifetime rate of attempted suicides and are prone to recurrent suicidality.[18,26,34–36] Bipolar patients with concurrent alcohol use disorders present with more severe psychopathology in acute mania, with a higher number of mood-related and manic symptoms, specifically with significantly higher mood lability and impulsivity, and higher rates of violent behavior.[37] Depression is particularly common among female bipolar patients with alcohol use disorders.[38] Female bipolar patients with alcohol abuse/dependence report more depressive symptoms as compared with either male bipolar alcoholics or both male and female nonalcoholic bipolar patients.[38]

TREATMENT CONSIDERATIONS IN PERSONS WITH COMORBID BIPOLAR DISORDER AND SUBSTANCE USE DISORDERS

Pharmacotherapy of Co-Occurring Bipolar Disorder and Substance Use Disorders

Minimal data are available from controlled studies on the pharmacotherapy of bipolar disorder and drug and alcohol use disorders. To date, 3 randomized, double-blind, placebo-controlled studies[39–41] have been conducted on the treatment of bipolar disorder comorbid with a substance use disorder (see Table 1). One of these studies[40] was conducted with adolescents, while the others examined adult samples.

Brady et al.[39] reported on carbamazepine treatment in cocaine-dependent individuals with (N = 57) and without (N = 82) affective disorders (including major depressive disorder or bipolar disorder) who were randomly assigned to receive either carbamazepine or placebo for 12 weeks. In the group of patients with affective disorders, there was a trend toward fewer cocaine-positive urine drug screens ($p = .08$) and a reduction in depressive symptom severity in carbamazepine-treated patients compared with placebo-treated patients. In individuals without affective disorders, carbamazepine treatment did not have a greater impact on cocaine use than placebo. The results of this study demonstrate that while some medications may be relatively ineffective in "pure" cocaine-dependent populations, the same medications may potentially be more effective in patients with bipolar disorder and cocaine dependence.

Geller et al.[40] conducted a 6-week, randomized, double-blind, parallel-group, placebo-controlled trial of lithium in 25 adolescents with bipolar I or II disorder or recurrent major depressive disorder with adolescent predictors of future bipolar diagnosis (such as delusions, switching to bipolar disorder during tricyclic antidepressant treatment, marked psychomotor retardation, and bipolar disorder in a first-degree relative) and comorbid substance abuse (primarily of alcohol or marijuana). Mean age at onset of bipolar disorder in the study was 9.4 years for bipolar I and 11.1 years for bipolar II. Mean age at onset of substance dependence was 15.3 years. The study produced encouraging results for both disorders: those taking lithium had significantly decreased urine drug screens than placebo subjects; subjects taking lithium also improved on Children's Global Assessment Scale compared with the placebo subjects.

Recently, Salloum et al.[41] evaluated the efficacy of valproate in 59 alcohol-dependent bipolar I patients in a 24-week, double-blind, placebo-controlled study. The participants were randomized to receive either valproate plus treatment as usual (which constituted lithium and psychosocial treatment) or placebo plus treatment as usual. Patients assigned to the valproate group had significantly fewer heavy drinking days and fewer drinks per drinking day than subjects assigned to placebo. Interestingly, there was no effect of valproate on manic or depressive symptomatology; however, changes in manic and depressive symptoms correlated with alcohol use outcomes. These findings suggest that valproate may have a positive effect on the reduction in alcohol consumption in bipolar patients independent of improvements in mood. The authors subsequently conducted a secondary analysis in 25 bipolar patients who reported marijuana abuse in addition to alcohol abuse.[42] Those in the marijuana abuse group were significantly more likely to present in the manic phase, had significantly more Axis I diagnoses, and had more severe alcohol and other drug abuse than patients without marijuana abuse. Valproate treatment appeared to decrease alcohol use in the marijuana abuse group compared with marijuana-abusing patients who did not receive valproate treatment. Thus, emerging, albeit limited and preliminary, data from placebo-controlled trials suggest that patients with bipolar disorder and substance dependence may respond favorably to pharmacotherapy.

Table 1. Medication Trials in Patients With Bipolar Disorder and Substance Use Disorder

Medication	Substance of Abuse	Psychiatric Disorder	Sample	Design	Findings
Randomized, double-blind, placebo-controlled trials					
Carbamazepine[39]	Cocaine	Major depressive disorder or bipolar disorder	N = 57 with affective disorder N = 82 without affective disorder	12-week, randomized, double-blind, placebo-controlled	Decreased cocaine use with carbamazepine compared with placebo in patients with an affective disorder/no effect of carbamazepine in patients without an affective disorder
Lithium[40]	Substance dependency on one or a combination of the following: marijuana, alcohol, cocaine, amphetamine, barbiturate, opiate, or benzodiazepine	Bipolar disorder or major depressive disorder with adolescent predictors of future bipolar diagnosis	N = 25 (adolescents)	6-week, randomized, double-blind, placebo-controlled	Fewer positive urine drug screens with lithium
Valproate[41]	Alcohol	Bipolar I	N = 59	24-week, randomized, double-blind, placebo-controlled	Decreased alcohol use with valproate
Open-label, randomized, controlled trial					
Quetiapine (initiated at baseline) or neuroleptic continuation[49]	Cocaine and amphetamine dependence and abuse	Bipolar I (N = 13) Schizoaffective disorder (N = 6) Schizophrenia (N = 3) Major depressive disorder (N = 2)	N = 29	12-week, open-label, randomized, controlled	Improved psychiatric symptoms, decreased drug craving in group receiving quetiapine
Open-label, nonrandomized trials					
Valproate[53]	Alcohol (N = 5) Polysubstance (N = 3) Cocaine (N = 1)	Bipolar disorder	N = 9	16-week, open-label	Significant improvement in both depression and mania compared with baseline Significant decrease in substance-use days compared with the month before valproate treatment
Lithium[52]	Cocaine	Bipolar spectrum disorder (hypomania and cyclothymia)	N = 10	12-week, open-label	Nonsignificant decrease in cocaine use (in 5 patients) Improved hypomania in 5 patients
Lamotrigine[54]	Cocaine	Bipolar I (N = 22) Bipolar II (N = 7) Bipolar NOS (N = 1)	N = 30	12-week, open-label	Significant improvements in HAM-D, YMRS, and BPRS Significant improvement in cocaine cravings (on CCQ; $p < .001$)
Lamotrigine[55]	Cocaine	Bipolar I (N = 51) Bipolar II (N = 15) Bipolar NOS (N = 7)	Enrolled, N = 73; ITT analysis, N = 62 (pooled data, 32 new patients + 30 patients from Brown et al, 2003)	Acute: 12-week, open-label Extension: 24-week, open-label	Significant improvements in HAM-D, YMRS, and BPRS Significant improvement in cocaine cravings (on CCQ; $p < .001$) and dollars spent on cocaine
Aripiprazole[51]	Alcohol, cocaine, opioids, cannabis	Bipolar I (N = 18) Bipolar II (N = 1) Schizoaffective disorder, bipolar type (N = 1)	N = 20	12-week, open-label	Improvement in mania and depression and some reduction in alcohol use and cocaine use
Quetiapine[50]	Cocaine	Bipolar I (N = 14) Bipolar II (N = 3)	N = 17	12-week, open-label	Significant improvements in HAM-D, YMRS, and BPRS Significant improvement in cocaine cravings (on CCQ) No change in urine drug screens

Abbreviations: BPRS = Brief Psychiatric Rating Scale, CCQ = Cocaine Craving Questionnaire, HAM-D = Hamilton Rating Scale for Depression, ITT = intent-to-treat, NOS = not otherwise specified, YMRS = Young Mania Rating Scale.

Few clinical trials have investigated the efficacy of atypical antipsychotics in dual-diagnosis patients, despite the mounting clinical evidence showing the efficacy of these agents in bipolar patients without substance abuse.[43–46] At least 2 possible explanations for the efficacy of atypical agents in dual-diagnosis patients can be postulated. First, they act on both dopaminergic and serotonergic systems. Clozapine, for example, enhances dopamine release in mesolimbic and mesocortical systems, which could decrease craving.[47] Serotonergic dysfunction has also been implicated in drug craving.[47] Thus, agents that have combined effects on serotonin and dopamine release (e.g., atypical antipsychotics) may be effective anticraving agents. Second, atypical agents are effective for both psychosis and mood symptoms[43–45,48] and may decrease drug use/craving secondary to improvement in psychiatric symptoms.

To date, there have been 3 studies conducted on the use of atypical antipsychotics in bipolar patients with substance use disorders[49–51] (see Table 1). Quetiapine was investigated in 2 studies of patients with bipolar disorder and cocaine dependence.[49,50] In the first of these studies, Brown and colleagues[49] evaluated the results of discontinuing typical antipsychotics and switching to the atypical antipsychotic quetiapine, or continuing on the typical antipsychotics in a 12-week, randomized, open-label study. Twenty-nine patients, 13 of whom were bipolar, were recruited for the study. Primary substance use disorders in these subjects were cocaine or amphetamine abuse or dependence. The quetiapine-treated group showed significant improvement in psychiatric symptoms and cocaine craving and a nonsignificantly greater reduction in cocaine use. Quetiapine was well tolerated, and patients randomized to quetiapine stayed in the study longer than the treatment-as-usual group.

In the second trial,[50] open-label, 12-week quetiapine add-on therapy was examined in 17 patients with bipolar disorder and cocaine dependence. Significant improvements in manic and depressive symptoms and in cocaine cravings were observed. Dollar amounts spent on cocaine and days of cocaine use decreased numerically, but the difference was not statistically significant.[50] Quetiapine was again well tolerated in this trial.

Brown et al.[51] examined aripiprazole, an atypical antipsychotic that acts as a dopamine-2 partial agonist, in 20 patients with bipolar disorder or schizoaffective disorder and a substance use disorder (primarily alcohol and cocaine). In patients actively using substances while on an antipsychotic, a switch from the antipsychotic to aripiprazole was associated with symptomatic improvements in mood and a reduction in substance use.[51] Data from these small open studies support the hypothesis that in dual-diagnosis patients atypical antipsychotic therapy may be associated with a reduction in drug use and craving and an improvement in psychiatric symptoms.

Several open-label studies with classes of medications other than antipsychotics were conducted in dual-diagnosis patients (see Table 1). Nunes et al.[52] gave lithium to 10 adult bipolar patients with cocaine abuse in an open fashion. While most patients showed some decrease in cocaine use, this finding did not reach statistical significance. Brady et al.[53] examined the use of open-label valproate in 9 bipolar patients with substance abuse, including 5 with alcohol dependence, 3 with polysubstance abuse, and 1 with cocaine dependence. Valproate (mean serum level 73 μg/mL) addition was associated with decreased symptoms of depression and mania and a significant decrease in the number of days of drug or alcohol use ($p < .005$), the amount of drug use, and the period of abstinence during the 16-week follow-up period.

Brown et al.[54] recently reported on the use of open-label lamotrigine in a group of patients ($N = 30$) with bipolar disorder and cocaine dependence. Lamotrigine significantly improved both manic and depressive symptoms in bipolar patients. Lamotrigine was associated with a reduction in craving for cocaine, the dollar amount spent on cocaine, and the number of days of cocaine use. The results of this first trial were duplicated in a replication and extension study with 32 patients.[55] These data were pooled for the 62 patients, and the results were reported for 12 weeks of acute treatment and for 24 additional weeks of the extension. Mania and depression scores improved significantly with lamotrigine treatment, as well as dollars per week spent on cocaine. Changes in psychiatric symptoms also significantly correlated with changes in cocaine use patterns.[55] These preliminary open studies show that lamotrigine may be a promising agent to be used in cocaine-dependent bipolar patients.

Psychotherapeutic Approaches to the Treatment of Co-Occurring Bipolar Disorder and Substance Use Disorders

Psychotherapeutic approaches to the treatment of bipolar patients with co-occurring substance use disorders have been reviewed in a number of recent publications[56–58] and will be only briefly summarized here.

To address the needs of persons with dual diagnoses, an integrated treatment approach was developed and introduced.[59] In this paradigm, both disorders are addressed simultaneously in the same treatment program. Patients receive comprehensive counseling and treatment of both disorders, which includes case management, vocational rehabilitation services, family counseling, housing, and medications. The treatment incorporates motivational strategies that prepare the patient for substance-free living.[59] The integrated treatment approach has been successfully utilized in dual-diagnosis bipolar/substance use disorder patients.[60] Although psychiatric symptoms of bipolar disorder improved modestly, the main efficacy was shown in terms of remission from substance abuse and in terms of improve-

ments in psychosocial functions (such as achieving independent living and improvements in employment).[60]

Two cognitive-behavioral approaches have been used in the treatment of dual-diagnosis patients. Weiss et al.[61,62] introduced Integrated Group Therapy, a treatment paradigm specifically developed for patients with bipolar and substance use disorders. This approach consists of 20 weekly group sessions, each session targeting a specific topic relevant to both disorders (e.g., "Managing bipolar disorder without abusing substances," "Taking medications"). During each session, participants discuss their mood, whether or not they were using drugs or alcohol, and their progress with their major goals. The Integrated Group Therapy approach has been tested in a 6-month pilot study with positive results.[63] Patients receiving Integrated Group Therapy remained abstinent longer than patients not receiving the treatment and were more likely to stay abstinent for 2 to 3 consecutive months.

Schmitz et al.[64] introduced a cognitive-behavioral approach specifically targeting dual-diagnosis patients with substance use disorders and affective disorders. This approach was tested in a 12-week randomized study against "medication monitoring" without cognitive-behavioral therapy (CBT) in patients with bipolar disorder and substance use disorders. In the medication-monitoring group, patients received individual sessions of about 20 minutes during regular study visits to discuss medication compliance, side effects, drug use, and mood symptoms. In the medication-monitoring-plus-CBT group, in addition to medication monitoring, patients also received 16 individual CBT sessions of about 60 minutes each. The CBT approach was specifically designed for dual-diagnosis patients. The authors found that while patients receiving CBT during their medication treatment did not improve significantly more than medication-monitoring patients on measures of substance use, there were significant improvements in medication compliance and depressive symptoms in the medication-monitoring-plus-CBT group.[64]

CONCLUSIONS

The treatment of patients with bipolar disorder and substance use disorders has been the topic of minimal investigation. This is unfortunate, as substance-related disorders appear to be more common in patients with bipolar disorder than any other Axis I illness and, when present, are associated with greater rates of hospitalization, violence toward self and others, and treatment nonadherence. To date, data from placebo-controlled, randomized studies are available on 3 agents: carbamazepine, lithium, and valproate. Overall, the data produced positive results. The use of atypical antipsychotics is a topic of interest to the field. To date, open-label data are available on only 2 antipsychotic agents, quetiapine and aripiprazole, in dual-diagnosis patients. Clearly, data from randomized, double-blind, placebo-controlled studies are needed before it will be possible to draw any conclusions on the efficacy of the atypical antipsychotics in bipolar populations with substance use disorders. Several psychotherapeutic interventions have been tried in dual-diagnosis patients with positive results, suggesting that integrated treatment models of pharmacotherapy and psychotherapy are useful in bipolar patients with substance use disorders.

Drug names: aripiprazole (Abilify), carbamazepine (Carbatrol, Equetro, and others), clozapine (Clozaril, FazaClo, and others), lamotrigine (Lamictal), lithium (Lithobid, Eskalith, and others), quetiapine (Seroquel).

Disclosure of off-label usage: The authors have determined that, to the best of their knowledge, aripiprazole is not approved by the U.S. Food and Drug Administration for the treatment of substance abuse; carbamazepine is not approved for the treatment of cocaine dependence; clozapine is not approved for the treatment of bipolar disorder; and lamotrigine, lithium, and quetiapine are not approved for the treatment of substance dependence.

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