Current Status of Co-Occurring Mood and Substance Use Disorders: A New Therapeutic Target

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Mood and substance use disorders commonly co-occur, yet there is little evidence-based research to guide the pharmacologic management of these comorbid disorders. The authors review the existing empirical findings, some of which may call into question current clinical pharmacotherapy practices for treating co-occurring mood and substance use disorders. The authors also highlight knowledge gaps that can serve as a basis for future research. The specific mood disorders reviewed are bipolar and major depressive disorders (either one co-occurring with a substance use disorder). Overall, findings from the relatively small amount of available data indicate that pharmacotherapy for managing mood symptoms can be effective in patients with substance dependence, although results have not been consistent across all studies. Also, in most studies, medications for managing mood symptoms did not appear to have an impact on the substance use disorder. In a recent trial for comorbid major depression and alcohol dependence, combination treatment with a medication for depression and another for alcohol dependence was found to reduce depressive symptoms and excessive drinking simultaneously. However, research has only begun to address optimal pharmacologic management of co-occurring disorders. In addition, current clinical treatment for alcohol and drug dependence often excludes new pharmacotherapies approved by the U.S. Food and Drug Administration for treating certain types of addiction. With new data becoming available, it appears that we need to revisit current practice in the pharmacological management of co-occurring mood and substance use disorders.

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The co-occurrence of mood and substance use disorders is common (1, 2), and numerous reports describe patients with both types of disorder as clinically more severe and more difficult to keep well compared with patients who have either problem alone (3). Typically, these patients are treated for either their mood disorder or their substance use disorder before receiving treatment for the other disorder (4). This approach follows from the long-standing clinical perspective that treating the primary disorder can often resolve other problems, or that one disorder will be easier to treat if the other is in remission (5).

Today, however, there are a growing number of clinical programs for patients with co-occurring disorders that integrate treatment for substance dependence with treatment for another psychiatric disorder (6). Nonetheless, little empirical work has been done to provide guidelines for prescribing pharmacotherapy for patients who have both a mood and a substance use disorder. This is partly due to an overall reluctance to prescribe pharmacotherapy for patients with drug and alcohol dependence for fear that they will experience drug-drug interactions, potentially overdose, or acquire additional dependencies on prescribed medications. Also, there continues to be a stigma associated with substance-dependent persons taking medications for drug and alcohol problems (7).

Currently, the usual treatment in the United States for a substance use disorder is psychosocial treatment. It is not typical to include pharmacotherapy for reducing substance use, even though the U.S. Food and Drug Administration (FDA) has approved medications for treating alcohol, opiate, and nicotine dependence (7). One common clinical approach has been to ask patients with co-occurring mood and substance use disorders to reduce or stop their substance use when they start treatment, thus allowing a determination of the extent of affective symptoms in the absence of substance use. This can be helpful in deciding whether to pharmacologically treat what appears to be major depression (8). However, it is difficult for some patients to reduce their substance use as they begin treatment. Delaying treatment of the mood disorder, as well as continued alcohol and drug use, can have unwanted consequences. For example, the patient may become suicidal, manic, or paranoid or may lose hope for recovery and abandon treatment altogether (4, 9, 10). However, there have been exceptions: van Zaane and

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colleagues (11) reported that continued excessive alcohol use in patients receiving treatment for bipolar disorder had no adverse effects on treatment outcomes.

A growing number of empirical treatment studies have evaluated the utility of prescribing a single medication or a combination of medications to reduce both mood symptoms and substance use. A recent well-controlled study (12) in which depressed alcohol-dependent patients were treated with a combination of an opioid antagonist to reduce drinking (naltrexone) and an antidepressant (sertraline) found a significantly greater remedial effect on drinking and mood with the combination treatment than with placebo or either medication alone.

In this review, we assess the current empirical status of pharmacological approaches for treating co-occurring mood and substance use disorders, based on available data from double-blind placebo-controlled trials. We concentrate here on pharmacotherapy and do not evaluate the use of psychosocial treatments. Also, we target the co-occurrence of substance use disorders with mood disorders and do not evaluate other types of psychiatric comorbidity.

Prevalence of Co-Occurring Mood and Substance Use Disorders

Estimates of the lifetime prevalence of mood and substance use disorders and the comorbidity of these disorders in the general population can be derived from two nationally representative large-scale surveys using DSM-IV diagnostic criteria: the National Epidemiologic Survey on Alcoholism and Related Conditions, which surveyed 43,093 people in 2001 and 2002 (1, 13); and the National Comorbidity Survey Replication, which surveyed 9,282 people in 2001 and 2003 (2, 14). The lifetime prevalence of bipolar spectrum disorders (bipolar I and II disorders and subthreshold bipolar disorder) is estimated to be approximately 4.4%. For major depressive disorder, lifetime prevalence estimates range from 13.2% to 16.6%. Based on distributions of age at onset, the projected lifetime risk at age 75 is higher, with estimates of 5.1% for bipolar I and II disorders and 23% for major depressive disorder.

Comorbidity of these disorders with substance use disorders (abuse and dependence) is substantially greater. As is known clinically, it is highest with bipolar disorder. The lifetime prevalence rate of any bipolar disorder and any substance use disorder is 47.3%, and for bipolar I disorder and any substance use disorder, 60.3%. Comorbid substance use disorder is also high in major depression, with lifetime rates of 40.3% for any alcohol use disorder and 17.2% for any drug use disorder. For major depression and alcohol dependence, the lifetime rate is 21%.

Clinical Features and Pharmacological Treatment

Compared with the extensive medical case-summary literature, only a modest amount of scientific data are available on the clinical features and the pharmacological treatment of patients with co-occurring mood and substance use disorders. Moreover, bipolar disorder and major depressive disorder differ not only in clinical presentation, but also in diagnostic-specific concerns and treatment outcomes. In the next sections, we discuss some of the differences, as well as the similarities, between substance-dependent patients with co-occurring bipolar disorder and those with co-occurring major depressive disorder.

Diagnostic Difficulties

In persons with co-occurring mood and substance use disorders, DSM-IV criteria indicate that the mood disorder is primary if it is not due to the effects of alcohol or drugs. Mood disorder symptoms should have been present prior to the patient's substance problem and/or should persist during abstinent periods. All other occurrences of mood disorder symptoms, according to DSM-IV, are likely "substance induced." This distinction can be made through a comprehensive clinical history that focuses on distinguishing a primary from a substance-induced mood disorder (8).

It has been commonly thought that identifying the etiology of a depressive disorder in substance-dependent patients is important for determining the course of the illness and the optimal treatment approach. For example, in major depression, when depressive symptoms persist after the substance problem has been treated, antidepressant treatment seems warranted (15). In cases where the mood disorder seems to fuel the substance use disorder, pharmacotherapy to alleviate mood symptoms may have a positive impact on the substance use disorder (16).

In cases where the mood disorder symptoms are solely a result of alcohol or drug use, the question arises as to whether a medication for a mood disorder would have any therapeutic impact beyond what abstinence from alcohol and drugs would achieve, since in many cases mood-related symptoms will spontaneously dissipate with reduction or cessation of substance use (8). In such cases, the use of antidepressant pharmacotherapy would likely be unnecessary, costly, and burdensome to the patient.

Finally, while mood-related symptoms may precede or be precipitated by drug and alcohol dependence, implying causation, there also may be common risk factors for mood and substance use disorders—such as stressful events, psychological trauma, and genetic vulnerability—that lead to co-occurring expression, without one disorder causing the other (17). In fact, the high incidence of substance use in persons with bipolar illness lends support to multiple pathways of causality.

While it is commonly known that patients with all types of co-occurring mental health issues and substance dependence can be clinically complicated and pose a formidable challenge to the treatment community, much of the available empirical pharmacological trial data on

co-occurring mood and substance use disorders focus on patients with diagnoses of major depressive disorder and alcohol dependence. What we have learned from the small number of controlled studies may not apply to persons with substance dependence co-occurring with other psychiatric illnesses.

In the case of major depression and alcohol dependence, each diagnosis alone carries a significant risk for the development of the other (1, 2, 18, 19), and patients with this comorbidity will have multiple problems, often additive from each of the disorders. While findings have not always been consistent, it has been shown that greater severity in one of these disorders can be associated with greater severity in the other (18, 20); that alcohol dependence may prolong the course of depression (21); and that depression that persists with abstinence from alcohol can be a risk factor for relapse to drinking (22, 23). Untreated depression can result in further problems, including increasing the potential for suicide (24). In addition, these patients tend to have other medical, psychiatric, and substance use comorbidities, including nicotine dependence (25). They also tend to have considerable psychosocial disability and increased utilization of health care resources, including psychiatric hospitalizations (26).

Pharmacotherapy for Co-Occurring Mood and Substance Use Disorders

Several fundamental questions arise in clinical practice when considering the pharmacological treatment of patients with co-occurring mood and substance use disorders. Does a medication given for a mood disorder affect the substance use disorder? Are medications that target mood disorders as effective in patients with mood disorders and comorbid substance dependence? How influential is knowing whether depression is primary or substance-induced in deciding whether to prescribe pharmacotherapy for depression, given that more than one study (22, 27) has demonstrated an antidepressant advantage for treating substance-induced depression? Should medication combinations be considered in patients with more than one disorder?

Treating Bipolar Substance-Dependent Patients With Mood Disorder Medications

There is a paucity of pharmacotherapy research focused exclusively on patients with bipolar illness and comorbid substance dependence. Bipolar disorder medication trials have typically excluded individuals with substance dependence. However, in the past decade, at least six published double-blind placebo-controlled trials have targeted adults with co-occurring bipolar and substance use disorders. (The few trials in which bipolar patients were a minority in the study group or in which outcomes were indistinguishable from those of other types of depressed patients were not included in this review; for example, see Brady et al. [28].)

Alcohol was the primary substance in five of the six trials, and the remaining study focused on cocaine use. The typical research paradigm for studying pharmacotherapy in these trials was to give a double-blind medication, primarily to treat the substance dependence after the patient was stabilized on a medication for the bipolar illness. In some cases, the double-blind medication was also a treatment for bipolar disorder, such as valproate (29) or quetiapine (30, 31); in other cases, it was an FDA-approved medication for treating alcohol dependence, such as naltrexone (32) or acamprosate (33); and in one case it was a nutritional supplement—citicoline (34)—that was evaluated for reducing cocaine use. Typically, these trials not only evaluated the medication's efficacy compared with placebo in reducing substance use, but also assessed any further reduction in mood symptoms that the double-blind medication might provide beyond any medication patients were taking for their mood disorder.

Results of the trials revealed that no additional benefit was achieved in reducing either depressive or manic symptoms (29, 31–34), with one exception: patients with bipolar disorder taking quetiapine in addition to treatment as usual showed a reduction in depressive symptoms compared with placebo treatment (30), although this finding was not replicated (31). Failure to show a differential response to depression in bipolar patients should not be surprising given the study design that is being used. In the majority of trials, the investigative medication was added to an accepted open-label regimen already provided for the mood symptoms.

Only two of the six trials showed a significant reduction in substance use: one using valproate to reduce drinking (29) and the other using citicoline to reduce cocaine use (34). There were nonsignificant trends in the direction of reducing drinking behaviors in two other studies, one with naltrexone (32) and one with acamprosate (33). Compared with the placebo group, the valproate group demonstrated significant reductions in the proportion of heavy drinking days, drinks per day, and drinks per heavy drinking day, especially when medication adherence was considered. These findings were validated by serum valproate levels. In the citicoline trial, cocaine-positive urine screens at the end of the trial were 6.4 times higher in the placebo group than in the citicoline group.

When only the mood disorder responds to treatment, it is important to determine the effect the substance use disorder may have on the recovery of the mood disorder. Some studies have demonstrated the ill effects on recovery from bipolar illness when the substance use disorder goes untreated (e.g., 35), while others have not found this to be the case (11, 36, 37). Although study design issues may explain some of the differences in findings, the sequence of syndrome emergence and the age at onset of

bipolar disorder may offer some explanation. In one study (36), there was no association between mood and substance use symptoms for patients in whom the substance use disorder preceded the bipolar disorder. However, in the same study, there was an association between mood and substance use symptoms for patients who had an early onset age for the bipolar disorder. In a large multicenter study (38), the distinction between primary and secondary substance use was not validated when the age at onset of the bipolar disorder was controlled for. Therefore, age at onset of bipolar disorder may be the most salient factor in understanding whether or not there will be a negative relationship between mood and substance use symptoms in patients treated for bipolar illness (36, 38).

In summary, persons with co-occurring bipolar and substance use disorders are a difficult-to-treat population, and conducting research with this group can be particularly challenging. Pharmacotherapies have been studied in a handful of well-controlled trials in which patients whose mood disorder has been stabilized were treated with a double-blind medication. The medications studied included two that are generally used for bipolar symptoms (quetiapine and valproate), two for alcohol dependence (naltrexone and acamprosate), and one nutritional supplement (citicoline). In these studies, adding a medication to reduce substance use to a pharmacotherapy for treating bipolar disorder did not consistently reduce substance use in this patient group. However, because so few studies have been conducted, more research is needed before any firm conclusions can be drawn. Finally, prevention and treatment of the substance use disorder is especially indicated for patients with an early age at onset of a bipolar disorder.

Treating Depressed Substance-Dependent Patients With Antidepressants

Treating depressed substance-dependent patients with antidepressants has not yielded consistent outcomes in alleviating depression, and these medications usually do not directly affect the substance use (16, 39). Thus, we need to know under what conditions prescribing antidepressant medications results in the best outcomes for depressed patients with substance dependence.

Antidepressants can be life-saving in individuals who are at risk for suicide or are severely debilitated by their depression. For decades, we have treated patients with major depression successfully with antidepressants, whether or not the patients have a co-occurring substance use disorder. However, because the studies that supported FDA approvals for antidepressants excluded patients with substance dependence, scientific inquiry has not adequately addressed whether antidepressants are efficacious in the treatment of depression in patients who also are substance dependent (40).

Major depression and drug dependence. Only a small number of double-blind placebo-controlled trials of depressed patients dependent on drugs have been published, primarily with patients dependent on opiates (41) and on cocaine (4, 42). Findings across these studies were inconsistent on alleviation of depressive symptoms by antidepressant medication. However, in a meta-analysis that combined these studies' results with those from similarly designed alcohol studies to evaluate antidepressant response in depressed patients with co-occurring drug or alcohol dependence, the conclusion was that antidepressants had a modest beneficial effect for patients with combined major depression and a substance use disorder (39).

Major depression and alcohol dependence. Evaluating the usefulness of antidepressants in treating depressed patients with co-occurring alcohol dependence has a long history, but only in the past decade have well-controlled trials been conducted. Historically, chronic drinkers were denied medications (except for detoxification) because of safety concerns about the potential interaction of medications with alcohol or the potential for antidepressant overdose in depressed alcoholics. Also, in early investigations (in the 1970s and 1980s) of antidepressant treatment for depressed alcohol-dependent patients, results showed that depressive symptoms were not alleviated. These studies were later criticized for their failure to provide an adequate course and dosage of antidepressants. Subthreshold daily doses were common in early trials because the study patients did not take many of the prescribed pills or could not tolerate what was prescribed. Some studies deliberately used lower dosages out of concern that depressed alcoholics might drink during treatment and experience unsafe medication-alcohol interactions or that they might be overly sensitive to medication side effects and stop treatment (e.g., 16). Theoretically, the opposite approach, in which the daily dose was raised to what was maximally tolerated, might have yielded better outcomes. That is, chronic drinking accelerates clearance of tricyclic antidepressants and potentially other drug classes, and it is also likely associated with an increased activation of liver microsomal enzymes, which continues over weeks of abstinence (42, 43).

More recently, double-blind placebo-controlled studies investigating pharmacotherapies for co-occurring depression and alcohol dependence have used either a tricyclic antidepressant or a selective serotonin reuptake inhibitor (SSRI). Based on the safety profile of SSRIs, investigators have been more willing to examine the efficacy of these medications in substance-dependent patients (44), including those with depression (16, 39). Conclusions drawn for patients with depression were that both tricyclics and SSRIs alleviated depression in most but not all cases, but they had little effect, direct or otherwise, on reducing drinking. A review that examined eight double-blind placebo-controlled trials of antidepressants (and

counseling) for patients with a depressive disorder and alcohol dependence (16) reported that six of the studies (75%) found a relationship between the medication and reductions in depressive symptoms, irrespective of type of antidepressant. Only three of the eight studies (38%) found an advantage for the medication over placebo in reducing drinking. In two studies, the antidepressant reduced both depressive symptoms and amount of drinking in depressed alcoholics, one with a tricyclic (desipramine) in alcohol-dependent patients with secondary depression (43), and the other with an SSRI (fluoxetine) in alcohol-dependent patients with primary depression and suicidal ideation (45). A large multisite trial (N=345) has since been conducted in which patients with major depression and alcohol dependence were treated with sertraline at 50–150 mg/day for 10 weeks. The study found no advantage of sertraline over placebo for alleviating depression or for reducing drinking (46). These surprising results may have been due to lower depression severity in that trial's sample than in those of other studies or to a large placebo response (see the meta-analytic review by Nunes and Levin [39]). Nonetheless, because of the trial's size, the results challenged the findings of some of the previous smaller trials that had suggested that depressed patients with a substance use disorder benefit from antidepressant medications.

New Treatment Strategy: Combining an Antidepressant and an Opioid Antagonist

Because antidepressants alone do not typically appear to affect drinking in depressed alcohol-dependent patients, a medication that directly affects drinking, such as naltrexone, may be an important adjunct to antidepressant therapy for an overall successful response to treatment. This possibility led our group to conduct a 14-week double-blind placebo-controlled trial (12) with 170 patients with major depression and alcohol dependence to evaluate the combination of two FDA-approved medications, one for depression (sertraline, up to 200 mg/day) and one for alcohol dependence (naltrexone, up to 100 mg/day). All patients received weekly cognitive-behavioral therapy. Depressive symptoms and amount of drinking were evaluated for each medication singly prescribed and for the medication combination, compared with placebo. We found that patients treated with the combination of sertraline and naltrexone achieved more abstinence from alcohol, delayed relapse to heavy drinking, and had a lower likelihood of being depressed at the end of treatment compared with those treated with sertraline or naltrexone alone or with placebo. These results await replication. It will also be important to evaluate other antidepressants in combination with other medications that have been found to be effective in treating alcohol dependence. Finally, future studies should investigate how long these medications should be continued once symptoms have remitted.

Future Directions

Our biggest challenge today in evaluating best practices for treating co-occurring mood and substance use disorders, surprisingly, is that few clinicians are prescribing medications to treat alcohol dependence, despite the fact that four medications are FDA-approved for it. We recognize that some clinicians are still unwilling to prescribe any medication when treating substance dependence, citing concerns about further abuse of the treatment drug. Fortunately, clinician bias is fading as scientists learn more about treating the addicted brain with certain nonaddictive medications that are meant to correct the neurobiology of addiction.

In addition, the population of substance-dependent patients represents considerable diversity in etiology, clinical presentation, and response to treatment. This may also explain inconsistent findings across the handful of available double-blind studies. There is a long-standing tradition of attempts to identify more homogeneous subgroups—for example, patients with alcohol dependence—and match treatments to subgroup characteristics. Targeting patients with co-occurring disorders is one attempt to differentiate a selected, more homogeneous subgroup of patients. It is likely, however, that these diagnostically discriminating subgroupings will require further subdivision to ensure well-matched treatments.

A very promising line of research has focused on genetic factors that may affect medication treatment response. For example, a number of functional polymorphisms have been studied in the gene encoding for the μ-opioid receptor, OPRM1. Particular interest has been focused on the Asn40Asp polymorphism (47); individuals with one or two copies of the Asp40 allele report greater subjective effects from alcohol, including feelings of intoxication, stimulation, sedation, and euphoria, compared with individuals who are homozygous for the Asn40 allele. Furthermore, in a retrospective analysis combining three clinical trials, patients with the Asp40 allele who were treated with naltrexone were 3.5 times less likely to relapse to heavy drinking (48). A recent review by Ray and colleagues (47) presented converging lines of research demonstrating the potential influence that the Asn40Asp polymorphism may have on the etiology and treatment response of alcohol dependence.

Along this same line of inquiry, Kranzler and colleagues (49) reported that a 5-hydroxytryptamine transporter-linked promoter region genotype together with age at onset of problem drinking had an impact on response to sertraline treatment (to reduce excessive drinking) in nondepressed alcohol-dependent patients. Essentially, while late-onset-age alcohol-dependent patients reduced their drinking with sertraline treatment, the sertraline response of the early-onset-age patients depended on a functional polymorphism in the serotonin transporter gene; in fact, one specific patient subgroup was actually

likely to drink more with sertraline treatment than with placebo.

Other promising typologies based on clinical characteristics have also been proposed as a way to match optimal treatments to alcohol subtype with the goal of improving treatment response rates in alcohol-dependent patients (e.g., 50). All of these unique classification systems, including genetically based ones, have yet to be applied to alcohol-dependent patient populations with co-occurring psychiatric disorders, and they have not been studied in drug-dependent patients who are not dependent on alcohol.

In the treatment of patients with bipolar disorder and co-occurring substance dependence, the typical design includes the stabilization of psychiatric symptoms before treating the substance use disorder with an additional medication. Thus, the few published double-blind placebo-controlled trials have "added on" other medications (sometimes another mood stabilizer) to assess their efficacy in treating the patient's substance dependence. This type of design has its limitations, and it does not allow the flexibility needed to evaluate investigative medications for mood and substance abuse outcomes independently of other medications the patient is already taking to treat the mood disorder. In this regard, adaptive treatment designs may be more apt for studying pharmacotherapy for persons with bipolar and substance use disorders.

In the case of co-occurring cocaine dependence, there continues to be a pressing need for viable medical treatments of cocaine dependence to be indicated as add-on treatments. Finally, we need more research on the course of illness in each of the co-occurring disorders when only one of them responds to treatment.

Conclusions

Empirical data that support effective pharmacological treatments for treating both the mood and the substance use disorder in patients with co-occurring disorders are long overdue. Co-occurrence prevalence rates are formidable, and patients with comorbid mood and substance use disorders often have more severe illness that is difficult to manage compared with either a mood or a substance use disorder alone. While we have been clinically treating such patients for decades, empirical evidence to support best practices in pharmacotherapy is lacking. Our treatment models for mood disorders and those for substance use disorders are well developed and detailed, but we do not know if they are applicable to persons with co-occurring mood and substance use disorders because practically all research has focused on single, not multiple disorders.

In most of the systematic pharmacotherapy trials that have been conducted to date with patients who have both a mood and a substance use disorder, patients were given a single medication for their mood disorder, and in some cases alcohol and drug counseling was provided. Both mood and drinking outcomes were evaluated. Overall, results from these studies have been inconsistent in establishing the effectiveness of mood-resolving medications to reduce mood symptoms and substance use. For most but not all studies, mood symptoms were effectively treated. However, in persons for whom bipolar disorder symptoms were resolved with mood-stabilizing medications, or symptoms of major depression with antidepressants, substance use typically was not affected by the medication, alcohol or drug use continued. Sometimes this affected recovery from the mood disorder (35), and in other cases it did not (36, 37).

One of our goals in this review was to bring together the existing empirical pharmacological data on treating persons with co-occurring disorders in order to determine exactly what we know in comparison to current clinical practices in treating these individuals. We also wish to promote the emerging view that the co-occurrence of a substance use disorder and another psychiatric disorder in all likelihood needs its own distinct treatment plan. We identified research supporting the approach of combining two pharmacotherapies, one for mood symptoms and another for substance dependence. Although we believe this approach could be a model for future clinical practice, it requires further research. Scientific inquiry has only begun to address this relatively neglected treatment area and to recognize the challenges in identifying the best treatment approach for co-occurring substance dependence and other psychiatric disorders.

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Clinical Guidance: Co-Occurring Mood and Substance Use Disorders

An emerging approach to treating comorbid mood and substance use disorders is simultaneous pharmacologic treatment of each. Patients with both types of disorders often have severe illness that is more difficult to manage than either one alone. Treatment for the mood disorder often improves mood symptoms but not alcohol or drug use. Pettinati et al. point to FDA-approved medications specifically for alcohol and opiate dependence. Their previous study of sertraline plus naltrexone, in addition to cognitive-behavioral therapy, showed greater effects on both depression and alcohol use from the combined medications than from either alone (Am J Psychiatry 2010; 167:668). Co-occurring bipolar and substance use disorders are difficult to treat; adding a medication for the substance disorder to a bipolar disorder treatment does not consistently decrease use. However, treating the substance use disorder is especially indicated for patients with an early onset of bipolar disorder.