Assessment and treatment of mood disorders in the context of substance abuse

Bryan K. Tolliver, MD, PhD; Raymond F. Anton, MD

Overview: the prevalence of comorbid mood disorders and substance use disorders

Affective disorders and substance use disorders (SUDs) are highly prevalent in the general population, and their co-occurrence is common.[1-7] In general, comorbid SUDs are associated with a significantly worse course of illness in both major depressive disorder (MDD)[8] and bipolar disorder,[9] each of which is known to be among the leading causes of global bur-

Recognition and management of mood symptoms in individuals using alcohol and/or other drugs represent a daily challenge for clinicians in both inpatient and outpatient treatment settings. Diagnosis of underlying mood disorders in the context of ongoing substance abuse requires careful collection of psychiatric history, and is often critical for optimal treatment planning and outcomes. Failure to recognize major depression or bipolar disorders in these patients can result in increased relapse rates, recurrence of mood episodes, and elevated risk of completed suicide. Over the past decade, epidemiologic research has clarified the prevalence of comorbid mood disorders in substance-dependent individuals, overturning previous assumptions that depression in these patients is simply an artifact of intoxication and/or withdrawal, therefore requiring no treatment. However, our understanding of the bidirectional relationships between mood and substance use disorders in terms of their course(s) of illness and prognoses remains limited. Likewise, strikingly little treatment research exists to guide clinical decision making in co-occurring mood and substance use disorders, given their high prevalence and public health burden. Here we overview what is known and the salient gaps of knowledge where data might enhance diagnosis and treatment of these complicated patients.

Dialogues Clin Neurosci. 2015;17:181-190.

Keywords: *addiction; alcoholism; bipolar disorder; comorbidity; dual diagnosis; major depressive disorder; suicide*

Author affiliations: Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, Charleston, South Carolina, USA

Address for correspondence: Bryan K. Tolliver, MD, PhD, Associate Professor, Addiction Sciences Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, Charleston, SC 29425, USA
(e-mail: tollive@musc.edu)

den of disease.[10] Long recognized clinically, the high prevalence of SUDs in those with mood disorders has been confirmed over the past 25 years in three large epidemiologic studies: the Epidemiologic Catchment Area (ECA) study,[11] the National Comorbidity Study (NCS),[12] and the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC).[1-3] Of these, the NESARC survey provides the most comprehensive, up-to-date data on psychiatric comorbidity. Whereas the ECA (n=20 291) and NCS (n=8098) surveys were based on *DSM-III* and *DSM-III-R* criteria, respectively, and did not measure substance dependence as a syndrome,[2] data from NESARC (n=43 093) indicate that the 12-month prevalence of *DSM-IV* independent mood disorders in the US population was 9.21% (12-month and lifetime prevalence of major depressive disorder [MDD] were 5.28% and 13.28%, respectively, whereas 12-month and lifetime prevalence of bipolar disorder were 2.0% and 3.3%)[1,2] and the rate of *DSM-IV* substance use disorders in the previous 12 months was 9.35%.[1] As in the ECA and NCS studies, the NESARC study found significant co-occurrence of mood disorders and SUDs whether considered in terms of lifetime or 12-month prevalence.[1-3] Among respondents with lifetime MDD, over 40% had an alcohol use disorder; 21% had a history of alcohol dependence, roughly 2-fold the rate in those without MDD. Among those with MDD in the prior 12 months, more than 14% had an alcohol use disorder, and 8.2% met criteria for alcohol dependence.[2] Similarly, among respondents with a past-year SUD, roughly 19.7% had at least one independent mood disorder during the same 12-month period.[1] Comorbid SUDs were particularly high in respondents with bipolar disorder, consistent with the ECA and NCS studies, both of which identified bipolar disorder as the Axis I diagnosis most associated with a co-occurring SUD.[11,12]

Two additional findings from NESARC were noteworthy for their diagnostic and treatment implications. First, fewer than 1% of individuals meeting criteria for a mood disorder in NESARC were classified as having substance-induced mood disorder (SIMD), a disturbance of mood that was exclusively attributable to substance use or withdrawal rather than an exacerbation of underlying MDD or bipolar disorder.[1] This result supported an earlier finding from the 1992 National Longitudinal Alcohol Epidemiologic Survey indicating that *prior, but not current* alcohol dependence increased the risk of current MDD more than 4-fold.[13] These results from two separate general population samples contradict previous data, acquired from almost 3000 treated alcohol-dependent subjects and their relatives, that had suggested that a significant proportion of mood disorder diagnoses were largely attributable to alcohol-induced affective symptoms.[14] Second, importantly, the proportion of respondents with independent mood disorders was significantly higher in treatment-seeking persons than in the overall sample. Specifically, among respondents with *DSM-IV* SUDs who sought substance abuse treatment in the past 12 months, the 12-month prevalence of co-occurring independent mood disorders was over 40%.[1]

The clinical implications of these findings from NESARC and earlier epidemiologic studies are clear and important. Independent mood disorders are common in individuals who use alcohol and drugs, especially in those seeking substance abuse treatment, and in many individuals the mood disturbance cannot be attributed to the acute effects of substance use or withdrawal. These results indicate that clinicians in addiction treatment settings must address co-occurring mood disorders, just as clinicians in primary care and mental health settings should assess for SUDs. This suggestion, however, does not mitigate the difficulty of differentiating between a substance-induced comorbid-state vs two independent but exacerbating conditions in the assessment of the dual-diagnosis patient. Further, the findings from NESARC suggest that treatment *should not be withheld* from substance-dependent individuals whose independent mood disorders are in remission on the assumption that mood symptoms are, or were, attributable to intoxication or withdrawal and thus must have resolved with abstinence.[1,2] The present review will further address these clinical implications separately with regard to their significance for diagnosis, course of illness and prognosis, as well as treatment. It is not intended to systematically compile and compare all literature on various SUDs (eg, alcohol use disorders vs cocaine, opioid, sedative, or cannabis use disorders), but rather will instead focus on current knowledge gaps and opportunities for advancement of research priorities, as well as improvement of clinical care as they pertain to assessment and treatment of mood disorders in the context of comorbid substance abuse.

Diagnostic challenges

Controversy regarding diagnosis has been a persistent impediment to progress in understanding the relationships between mood disorders and SUDs. Given the absence of validated clinical biomarkers for either MDD or bipolar disorders,[15] misdiagnosis of mood disturbance in the context of active substance abuse is a legitimate concern. It has long been appreciated that affective symptoms are common in substance-dependent patients in treatment but often change or resolve over time with lengthening abstinence.[16,17] This observation, as well as the fact that intoxication and/or withdrawal from alcohol and other drugs of abuse can induce states that mimic symptoms of independent mood disorders[18,19] complicate the diagnosis of MDD and bipolar disorders in patients with SUDs who are actively abusing substances at the time of assessment. Consequently, the importance of distinguishing independent (primary) mood disorders from substance-induced (secondary) mood disorders has long been emphasized[19] as both over- and underdiagnosis of mood disorders have been shown to occur in patients with SUDs.[20,21]

A traditional approach to the diagnostic dilemma is to withhold pharmacologic treatment for depression for a period of time after abstinence is established in order to determine whether, and to what extent, mood symptoms are attributable to substance use. By convention, treatment delay is often at least 1 month, consistent with the *DSM-IV* course specifier for early full remission from substance dependence and as described in Criterion C for Substance-Induced Mood Disorder in *DSM-IV*.[22] Unfortunately, delaying treatment for mood symptoms can be problematic for a number of reasons. First, patients may be unable to establish or sustain abstinence for a month or longer. In the case of substances like alcohol or benzodiazepines, establishing abstinence may require medically managed inpatient detoxification due to potentially life-threatening withdrawal. While this generally requires only a relatively short time in acute care settings depending on the complexity of withdrawal, after discharge patients often return to their home environment where the risk of relapse in the first 30 days is high. For instance, Kiefer and colleagues found that following inpatient detoxification (typically much longer in Europe than in the US), 65% of untreated subjects had consumed alcohol and 50% had returned to heavy drinking within 2 weeks of discharge.[23] Patients with untreated depression are at higher risk to return to drinking or drug use and tend to do so more quickly.

In a cohort of patients hospitalized for alcohol dependence who were followed monthly for 1 year after discharge, Greenfield and colleagues found that a diagnosis of major depression at inpatient treatment entry was associated with a shorter time to first drink (38 days vs 125 days) as well as a shorter time to full relapse (41 days vs 150 days) compared with patients without major depression at admission.[24] Furthermore, depressed alcohol-dependent subjects who were discharged without antidepressants were likelier to return to drinking than were their antidepressant-treated counterparts. Whereas virtually all depressed subjects discharged without antidepressants had relapsed in the first 100 days after discharge, 20% of those depressed subjects discharged on antidepressants remained abstinent at 1 year.[24] Interestingly, no statistically significant differences were found in time to first drink or relapse in depressed subjects who were initially classified as having independent MDD vs those classified as having substance-induced depression.[24] Similarly, Hasin and colleagues followed 250 inpatients with cocaine, heroin, or alcohol dependence at 6, 12, and 18 months after discharge from index hospitalization, roughly 60% of whom were diagnosed with co-occurring depression. Depressed patients were retrospectively classified into three subgroups: those with premorbid MDD prior to the development of substance dependence, those meeting criteria for MDD during sustained abstinence during follow-up, or those considered to have exclusively substance-induced depression.[25] The subjects with premorbid MDD or substance-induced depression were significantly more likely to meet criteria for substance dependence during the follow-up period. Of the patients (n=133) who did not use any substances for at least 26 consecutive weeks, those who experienced a major depressive episode during this time were subsequently three times as likely to relapse into dependence during the follow-up period.[25] Given these findings, it is especially concerning that substance-dependent patients with a history of major depressive episode(s) are significantly likelier to have attempted suicide regardless of whether the depression first occurred before or during substance use.[26] These data underscore the importance of collecting a comprehensive psychiatric history that addresses relative onset of mood symptoms and substance abuse in all patients

with SUDs, and also suggests that caution is warranted in withholding or delaying treatment in these patients.

Conversely, many people who have underlying alcohol and other substance use disorders present to primary care and/or mental health professionals with complaints of depression, anxiety, and insomnia. Here again a good history of alcohol and substance use is crucial but, as most clinicians recognize, many patients will not provide accurate information regarding the drinking and substance use, reducing diagnostic accuracy. Fortunately, in this case, laboratory tests including urine drug screens and urine/serum biomarkers of alcohol use can be helpful in establishing the appropriate diagnosis. While this is beyond the scope of this review, suffice it to say that there are three tests available that are useful to establish any recent alcohol use (urinary ethylglucuronide [EtG]), moderate to heavy use (phosphatidyl ethanol), and heavy harmful use,(carbohydrate deficient transferrin [%CDT]). Readers are referred to a salient review of this topic by Litten and colleagues.[27] In addition to these laboratory aids, clinicians should be suspicious of alcohol or drug abuse underlying psychiatric complaints when: (i) there is a past history of substance abuse; (ii) there is a family history of substance abuse; (iii) there are co-occurring or past medical disorders associated with alcohol or substance abuse (eg, GI conditions, trauma, HIV, HCV, macrocytic anemia, high uric acid, smoking); (iv) there are chronic pain complaints; (v) multiple relationship problems; (vi) numerous job changes; (vii) legal difficulties such as DUIs, public intoxication charges, and assault arrests including domestic violence.

Course of illness and prognosis

The interrelationships of diagnosis, prevalence, illness course, and treatment are fundamental to all medical practice but are especially important in the realm of psychiatric comorbidity. Accurate diagnosis is essential to understanding a given individual's prognosis as well as for formulating a treatment plan. Conversely, understanding the natural history of a given disease, and its likely responsiveness to treatment, may aid in diagnosing it accurately as individuals with the disorder(s) are longitudinally monitored and treated over time. For example, given the high prevalence of both depression and SUDs, it is reasonable to expect high rates of mood episodes that are attributable primarily or exclusively to substance use and that do not recur unless active substance use is resumed. However, this has not been found to be universal in either clinical samples[28,29] or in epidemiologic studies.[1,30] For instance, Ramsey et al found that over 25% of treatment-seeking alcoholics first diagnosed with SIMD at baseline were reclassified as having MDD over the following year of follow-up.[28] Similarly, in inpatients with alcohol, cocaine, or opioid dependence followed for 1 year after discharge, Nunes and colleagues reported that 57% met *DSM-IV* criteria for a major depressive episode.[29] Whereas 51% of the sample had initially been classified as having SIMD at admission, only 14% of depressed patients were classified as having SIMD at follow-up. Patients initially classified as having substance-induced depression at baseline were equally likely to have a major depressive episode during follow-up compared with those initially classified as having MDD; in the group of depressed patients as a whole, the mean number of weeks spent depressed over 12 months was 25.6 (SD 15.3).[29] Recent analysis of data from Wave 2 of NESARC, conducted approximately 3 years after the original survey, has allowed this question to be addressed in a nonclinical sample of over 2000 respondents who met lifetime criteria for MDD and SUD at Wave 1. Of the 106 respondents classified as having SIMD in Wave 1 (only 0.26% of depressed respondents with SUDs), 88 were resurveyed in Wave 2; of these, 95% of those who had experienced a depressive episode between Waves 1 and 2 were reclassified as having MDD.[31]

In the case of bipolar disorders and comorbid SUDs, the situation is particularly complex because: (i) the mood and substance illnesses are likely to exert bidirectional influences on each other; and (ii) they rarely occur alone in the individual patient in the absence of other comorbid psychiatric conditions, any of which may contribute to illness severity. For example, in bipolar disorder comorbid SUDs are associated with early age of onset,[32] high rates of smoking,[33] and frequent co-occurrence of anxiety disorders,[34-37] attention deficit/hyperactivity disorder,[38] and personality disorders,[39] each of which is associated with a more severe course of affective illness. Accordingly, it is difficult to know to what extent comorbid SUDs are contributory per se, but it is well established that alcohol and drug dependence are associated with poor clinical outcomes in patients with bipolar disorder. Though exceptions have been reported,[40,41] comorbid SUDs are associated with poor treatment adherence,[42] longer, more fre-

quent mood episodes,[43] more mixed manic-depressive episodes,[44-46] and lower functional recovery, even during abstinence,[47] suggesting that SUDs may be a marker rather than a determinant of bipolar illness severity. As a result, bipolar patients with SUDs have higher utilization of emergency services,[48] and more hospitalizations[49,50] compared with bipolar patients without SUD. Comorbid SUDs also predict poor response to lithium, a standard mood-stabilizing treatment of bipolar disorder.[46,51,52] Of particular concern, SUDs are often accompanied by increased impulsivity and suicidality in those with bipolar disorder[53,54]; in fact the risk of attempted suicide in bipolar alcoholics is almost twice that of non-alcoholic bipolar patients.[55-58] Tragically, 14% to 16% of those with bipolar disorder and co-occurring SUDs complete suicide.[59]

Despite the high prevalence of comorbidity of mood disorders and SUDs, prospective data regarding prognostic factors for either mood or substance use outcomes are sparse and somewhat inconsistent. Whereas most early prospective studies found that substance abuse was associated with increased syndromal mood recurrence and shorter time in remission in bipolar disorders,[60-64] other investigators have noted that spacing of follow-up visits in these studies tended to be long and quite variable, and that actual amounts of substance intake received little or no attention.[41]

Results of subsequent prospective research have been mixed. The 3-year course of 51 patients with bipolar disorder and comorbid SUDs enrolled in the New Hampshire Dual Diagnosis Study was characterized by substantial improvement in substance abuse outcomes (61% in full remission at 3 years) and functional status but only modest improvement in bipolar symptoms, with weak relationships among outcome domains.[65] In contrast, van Zaane and colleagues reported wide variability in alcohol use with no appreciable association with psychiatric symptoms or functional status among a cohort of bipolar alcoholics followed prospectively for 1 year.[41] More recently, Farren and colleagues found that drinking outcomes improved and depression severity generally lessened in alcohol-dependent patients with either MDD or bipolar disorder (as did mania severity in bipolar alcoholics) who were followed over 5 years.[66] This group found that there was no correlation between either depression severity (as measured by the Beck Depression Inventory [BDI]) or mania severity (as measured by the Young Mania Rating Scale [YMRS]) and abstinence or number of drinking days at 5 years, but that both BDI and YMRS scores were positively correlated with units of alcohol consumed per drinking day.[66] In this cohort, drinking outcomes at 5 years were best predicted by drinking outcomes at earlier time points and were not associated with age, gender, or mood diagnosis.

Unfortunately, these studies are unable to address a question that is likely to be relevant to clinicians treating patients who are early in recovery[67,68]: specifically, what are the relationships between the trajectories of mood symptoms and substance use in the near term? If patients remain abstinent, will mood outcomes improve automatically? Conversely, if mood stability is achieved, are substance use outcomes necessarily improved? Stated another way, does substance abuse precede depression[69] or vice versa? To address this question, two analyses of data from an 8-week randomized placebo-controlled trial of acamprosate in alcohol-dependent subjects with bipolar disorder were conducted by Prisciandaro and colleagues.[70,71] In the first analysis, comorbid anxiety disorders were prospectively associated with increased depressive symptoms and alcohol use over the 8-week trial period, as were the use of either antipsychotic or anticonvulsant medications.[70] In the second analysis, this group applied a novel statistical method (hidden Markov modeling) to assess week-to-week prospective relationships among depressive symptoms, alcohol craving, and alcohol use.[71] Contrary to previous work suggesting that depression is likely to be precipitated by alcohol use,[69] the latter study found that depressive symptoms and alcohol craving predicted proximal alcohol use 1 week later, whereas the reciprocal relationship was not observed.[71] Though these results were limited to alcohol use and require independent replication in a larger sample, they underscore the importance of addressing mood symptoms in addition to emphasizing abstinence in patients with co-occurring mood disorders and SUDs.

In summary, the relationship between the respective course of illness of co-occurring mood disorders and SUDs appears to be complex and incompletely understood at this time. As such, it may be wise to question assumptions about how mood and substance use disorders influence each other in given individuals or clinical populations as a whole. Considerably more research regarding course of illness is warranted given the obvious implications for treatment.

Treatment of co-occurring mood and substance use disorders

Traditionally the approach to treating SUDs in the Unites States has been psychosocial counseling, usually in a combination of group and individual settings. Though progress has been made in the development of integrated group therapy[72] and in application of established behavioral approaches such as contingency management[73] in patients with co-occurring SUDs and mood disorders, the present review will restrict the discussion to the current evidence base for pharmacotherapy in these patients. A number of critical questions encountered regularly in clinical practice remain unanswered regarding pharmacotherapy for comorbid mood and substance use disorders. For example, is it essential that the mood disorder be independent (primary) to benefit from mood-stabilizing medications or can those that also have substance-induced (secondary) mood symptoms benefit from these medication(s)? Should treatment of affective symptoms and substance abuse proceed simultaneously or in staged/sequenced fashion? If sequenced, in what order should treatment proceed? Can depression and/or mania be treated successfully in patients who continue to drink or use drugs heavily? Conversely, can patients with severe substance use disorders establish and maintain sobriety without adequate treatment of mood instability? Can any individual medications effectively treat both conditions, or are combinations of medicines necessary? Unfortunately, empirical data that may help address these important questions are sparse, in part because individuals with SUDs are traditionally excluded from medication trials for MDD and bipolar disorder, and likewise most clinical trials of agents for treating SUDs exclude other Axis I psychiatric conditions.[5-7]

In the case of patients with MDD and comorbid SUDs, the majority of previous research has focused on the use of antidepressants.[5] In the era predating the development of selective serotonin reuptake inhibitors (SSRIs), safety concerns regarding the potential for fatal overdose on tricyclic antidepressants or monoamine oxidase inhibitors impeded both research and clinical use of these drugs in depressed patients with comorbid SUDs. A 2004 meta-analysis by Nunes and Levin found that of clinical research focusing on comorbid SUD and mood disorders conducted at the time, only one third (14 of 44) of studies met criteria as adequately placebo-controlled, double-blind, randomized prospective clinical trials.[74] This meta-analysis found evidence for a modest beneficial effect of antidepressants on mood symptoms in depressed subjects with SUDs but noted high heterogeneity of effects across studies, with virtually no effects evident on substance use outcomes except in trials with depression effect sizes >0.5. As Nunes and Levin noted, a number of moderators of depression outcomes (eg, placebo response, sample characteristics, time of depression diagnosis, etc) were found, thereby preventing extrapolation between antidepressant efficacy and effects on substance use outcomes in these trials, either within or between studies included in the meta-analysis.[74] Pettinati reported similar findings in a review of antidepressant trials in depressed alcoholics, with 75% of the trials finding benefit for reduction of depressive symptoms but only a minority reporting beneficial effects on drinking outcomes.[75] Interestingly, a large multisite trial of sertraline (50 to 150 mg) that enrolled 345 alcohol-dependent subjects with MDD found no superiority of sertraline over placebo for either depression or drinking outcomes.[76] Importantly, this trial randomized based on secondary versus independent depression distinction and generally found no differences based on this classification.

More recently, Pettinati and colleagues reported a significant effect of the combination of sertraline with the opioid antagonist naltrexone, one of 3 FDA-approved medications for the treatment of alcohol dependence, in reducing drinking in depressed alcohol-dependent subjects.[77] In this trial, subjects were randomized to sertraline, naltrexone, the combination of sertraline plus naltrexone, or double placebo for 14 weeks while receiving weekly cognitive behavioral therapy. The group receiving the combination of sertraline and naltrexone had a significantly higher rate of abstinence (53.7%) that was in fact double that of the comparison groups (21.3% to 27.5%).[77] In addition, subjects in the combination group exhibited a significantly longer delay to relapse to heavy drinking than those in any of the comparison groups. Though differences in the improvement of depression scores among groups fell just short of statistical significance, this outcome also tended to favor sertraline plus naltrexone combination treatment. The combination therapy was well tolerated relative to the other treatment groups. The study by Pettinati et al[77] is a landmark in dual-diagnosis treatment research that may have immediate impact on clinical practice,

suggesting that treating both MDD and alcohol use disorder simultaneously with medications indicated for each condition should be a treatment standard—again emphasizing the need for good assessment and diagnosis. Also, while Pettinati et al did not investigate the psychotherapeutic/counseling component, it is likely that more than routine medication visits might be needed to successfully treat these comorbid patients. In another comorbid alcohol and MDD study, Moak et al[78] found that sertraline in combination with CBT (similar to that used in the Pettinati study) reduced drinks per drinking day compared with placebo and was particularly useful in reducing depression in women.

In the case of patients with bipolar disorder and comorbid SUDs, even less is known about optimal treatment because few randomized controlled medication trials have been conducted. At present, only nine clinical trials that assessed substance use as the primary outcome measure in this population have been published. Three of these trials evaluated subjects with bipolar disorder and stimulant dependence: one positive trial of lamotrigine for treatment of bipolar disorder and cocaine dependence[79] and one trial each of the nutritional supplement citicoline for treatment of bipolar disorder and cocaine dependence[80] and methamphetamine dependence,[81] respectively. The six other randomized controlled trials have studied subjects with bipolar disorder and co-occurring alcohol dependence, the SUD most commonly diagnosed in patients with bipolar disorder.[1,11]

Of these six trials, only one has demonstrated efficacy in reducing drinking. Salloum and colleagues found that valproate significantly reduced the proportion of heavy drinking days and drinks per drinking day in alcohol-dependent subjects with bipolar I disorder when added to lithium and counseling.[82] Three trials of quetiapine,[83-85] one trial of naltrexone,[86] and one trial of acamprosate[87] did not support the efficacy of these medications in bipolar alcoholics. Whether this is due to sample size effects, compliance issues, variability of concomitant mood stabilization treatment, or the nature of the comorbid illness (including genetic and other comorbid psychiatric symptoms) is unclear.

Finally, it is worth noting that the paucity of data from randomized clinical trials is not the only obstacle to advancing pharmacotherapy of comorbid mood disorders and SUDs. The potential use of addiction maintenance therapies such as buprenorphine for treatment-resistant depression has been of interest for over 20 years,[88] but has received little empirical study due in large part to concerns about abuse liability and physical dependence. Indeed, prevailing opinion of many treatment providers, patients themselves, and society as a whole continues to impede the use of *any* drug treatments for addiction in general. Consequently, adoption of medication-assisted treatment of SUDs in individuals with or without mood disorders remains disappointingly low in the United States.[89] Available data suggest that this is especially the case for patients with comorbid mood and substance use disorders. For example, of the large number of bipolar patients with SUDs who were enrolled in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD) study, only 0.4% were prescribed approved drug therapies for alcohol or opioid dependence at the time of enrollment.[90] Similarly, patients with bipolar disorder tend to have high rates of cigarette smoking and low rates of quit attempts,[91] yet few psychiatrists discuss smoking cessation with their patients and a notably smaller proportion combine counseling with approved treatments for nicotine dependence.[92,93]

Conclusions

Co-occurring mood disorders and SUDs are common, and tend to have an adverse impact on both mood and substance use outcomes. Diagnostic challenges remain common, though longitudinal clinical studies and large-scale epidemiologic studies conducted over the past two decades have begun to elucidate the prevalence and course of independent vs substance-induced mood disorders in patients with SUDs and have begun to pose questions about the appropriateness of withholding treatment in these patients. Much more research on prognosis and treatment of comorbid mood and substance use disorders is urgently needed. ❑

Acknowledgements: Dr Anton's research was supported by K05 grant number AA017435. Dr Tolliver's research was supported by K23 grant AA017666.

REFERENCES

1. Grant BF, Stinson FS, Dawson DA, et al. Prevalence and co-occurrence of substance use disorders and independent mood and anxiety disorders. Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry.* 2004;61:807-816.
2. Hasin DS, Goodwin RD, Stinson FS, Grant BF. Epidemiology of Major Depressive Disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2005;62:1097-1106.
3. Hasin DS, Stinson FS, Ogburn E, Grant BF. Prevalence, correlates, disability, and comorbidity of DSM-IV alcohol abuse and dependence in the United States: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *Arch Gen Psychiatry*. 2007;64:830-842.
4. Merikangas KR, Akiskal HS, Angst J, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey Replication. *Arch Gen Psychiatry*. 2007;64:543-552.
5. Pettinati HM, O'Brien CP, Dundon WD. Current status of co-occurring mood and substance use disorders: a new therapeutic target. *Am J Psychiatry*. 2013;170:23-30.
6. Farren CK, Hill KP, Weiss RD. Bipolar and alcohol use disorder: a review. *Curr Psychiatry Rep*. 2012;14:659-666.
7. Frye MA, Salloum IM. Bipolar disorder and comorbid alcoholism: prevalence rate and treatment considerations. *Bipolar Disord*. 2006;8:677-685.
8. Agosti V, Levin FR. The effects of alcohol and drug dependence on the course of depression. *Am J Addict*. 2006;15:71-75.
9. Tohen M, Greenfield SF, Weiss RD, Zarate CA, Vagge LM. The effect of comorbid substance use disorders on the course of bipolar disorder: a review. *Harv Rev Psychiatry*. 1998;6:133-141.
10. Murray C, Lopez A. Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study. *Lancet*. 1997;349:1436-1442.
11. Reiger DA, Farmer ME, Rae DS, et al. Comorbidity of mental disorders with alcohol and other drug abuse. *JAMA*. 1990;264:2511-2518.
12. Kessler RC, Crum R, Warner L, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. *Arch Gen Psychiatry*. 1997;54:313-321.
13. Hasin DS, Grant BF. Major depression in 6050 former drinkers: Association with past alcohol dependence. *Arch Gen Psychiatry*. 2002;59:794-800.
14. Schuckit MA, Tipp JE, Bergman M, Reich W, Hesselbrock VM, Smith TL. Comparison of induced and independent major depressive disorder in 2,945 alcoholics. *Am J Psychiatry*. 1997;154:948-957.
15. The Biomarkers Definitions Working Group of the National Institutes of Health. Biomarkers and surrogate endpoints: preferred definitions and conceptual framework. *Clin Pharmacol Ther*. 2001;69:89-95.
16. De Leon G, Skodol A, Rosenthal MS. Phoenix House: Changes in psychopathological signs of resident drug addicts. *Arch Gen Psychiatry.* 1973;28:131-135.
17. Brown SA, Schuckit MA. Changes in depression among abstinent alcoholics. *J Stud Alcohol.* 1988;49:412-417.
18. Schuckit MA. The clinical implications of primary diagnostic groups among alcoholics. *Arch Gen Psychiatry*. 1985;42:1043-1049.
19. Schuckit MA. Genetic and clinical implications of alcoholism and affective disorder. *Am J Psychiatry*. 1986;143:140-147.
20. Goldberg JF, Garno JL, Callahan AM, et al. Overdiagnosis of bipolar disorder among substance use disorder inpatients with mood instability. *J Clin Psychiatry*. 2008;69:1751-1757.
21. Albanese MJ, Clodfelter RC, Pardo TB, Ghaemi SN. Underdiagnosis of bipolar disorder in men with substance use disorder. *J Psychiatr Pract*. 2006;12:124-127.
22. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders.* 4th ed. Washington, DC: American Psychiatric Association; 1994.
23. Kiefer F, Holger J, Tarnaske T, et al. Comparing and combining naltrexone and acamprosate in relapse prevention of alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry.* 2003;60:92-99.
24. Greenfield SF, Weiss RD, Muenz LR, et al. The effect of depression on return to drinking: a prospective study. *Arch Gen Psychiatry.* 1998;55:259-265.
25. Hasin D, Liu X, Nunes E, McCloud S, Samet S, Endicott J. Effects of major depression on remission and relapse of substance dependence. *Arch Gen Psychiatry*. 2002;59:375-380.
26. Aharonovich E, Liu X, Nunes E, Hasin DS. Suicide attempts in substance abusers: Effects of major depression in relation to substance use disorders. *Am J Psychiatry*. 2002;159:1600-1602.
27. Litten RZ, Bradley AM, Moss HB. Alcohol biomarkers in applied settings: recent advances and future research opportunities. *Alcohol Clin Exp Res*. 2010;34(6):955-967.
28. Ramsey SE, Kahler CW, Read JP, Stuart GL, Brown RA. Discriminating between substance-induced and independent depressive episodes in alcohol-dependent patients. *J Stud Alcohol*. 2004;65:672-676.
29. Nunes EV, Liu X, Samet S, Matseoane K, Hasin D. Independent versus substance-induced major depressive disorder in substance-dependent patients: Observational study of course during follow-up. *J Clin Psychiatry*. 2006;67:1561-1567.
30. Blanco C, Alegria AA, Liu SM, et al. Differences among major depressive disorder with and without co-occurring substance use disorders and substance-induced depressive disorder: Results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2012;73:865-873.
31. Magidson JF, Wang S, Lejuez CW, Iza M, Blanco C. Prospective study of substance-induced and independent major depressive disorder among individuals with substance use disorders in a nationally representative sample. *Depress Anxiety*. 2013;30:538-545.
32. Perlis RH, Miyahara S, Marangell LB, et al. Long-term implications of early onset bipolar disorder: data from the first 1000 participants in the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). *Biol Psychiatry*. 2006;55:875-881.
33. Heffner JL, Strawn JR, DelBello MP, Strakowski SM, Anthenelli RM. The co-occurrence of cigarette smoking and bipolar disorder: phenomenology and treatment considerations. *Bipolar Disord*. 2011;13:439-53.
34. Simon NM, Otto MW, Wisniewski SR, et al. Anxiety disorder comorbidity in bipolar disorder patients: data from the first 500 participants in the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Am J Psychiatry*. 2004;161:2222-2229.
35. MacKinnon DF, Zamoiski R. Panic comorbidity with bipolar disorder: what is the manic-panic connection? *Bipolar Disord*. 2006;8:648-664.
36. Goldstein BI, Levitt AJ. The specific burden of comorbid anxiety disorders and of substance use disorders in bipolar I disorder. *Bipolar Disord*. 2008;10:67-78.
37. Alegria AA, Hasin DS, Nunes EV, et al. Comorbidity of generalized anxiety disorder and substance use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2010;71:1187-1195.
38. Nierenberg AA, Miyahara S, Spencer T, et al. Clinical and diagnostic implications of lifetime attention-deficit / hyperactivity disorder comorbidity in adults with bipolar disorder: Data from the first 1000 STEP-BD participants. *Biol Psychiatry*. 2005;57:1467-1473.
39. Zimmerman M, Morgan TA. The relationship between borderline personality disorder and bipolar disorder. *Dialogues Clin Neurosci*. 2013;15:155-169.
40. Ostacher MJ, Perlis RH, Nierenberg AA, et al. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: Prospective data from the systematic treatment enhancement program for bipolar disorder (STEP-BD). *Am J Psychiatry*. 2010;167:289-297.
41. van Zaane J, van den Brink W, Draisma S, Smit JH, Nolen WA. The effect of moderate and excessive alcohol use on the course and outcome of patients with bipolar disorders: a prospective cohort study. *J Clin Psychiatry*. 2010;71:885-893.
42. Manwani SG, Szilagyi KA, Zablotsky B, Hennen J, Griffin ML, Weiss RD. Adherence to pharmacotherapy in bipolar disorder patients with and without co-occurring substance use disorders. *J Clin Psychiatry*. 2007;68:1172-1176.
43. Schneck CD, Miklowitz DJ, Calabrese JR, et al. Phenomenology of rapid-cycling bipolar disorder: data from the first 500 participants in the Systematic Treatment Enhancement Program. *Am J Psychiatry*. 2004;161:1902-1908.

Evaluación y tratamiento de los trastornos del ánimo en el contexto del abuso de sustancias

El reconocimiento y manejo de los síntomas anímicos en los sujetos que emplean alcohol y/u otras drogas es un desafío diario para los clínicos en el tratamiento tanto de pacientes ambulatorios como hospitalizados. El diagnóstico de los trastornos del ánimo que están a la base de un abuso de sustancias requiere de una recopilación cuidadosa de la historia psiquiátrica, y a menudo es clave para lograr una planificación terapéutica y resultados óptimos. Una falla en el reconocimiento en estos pacientes de la depresión mayor o de los trastornos bipolares puede traducirse en un aumento en la frecuencia de recaídas, recurrencias y episodios anímicos, y un riesgo elevado de suicidio consumado. Durante la última década la investigación epidemiológica ha clarificado la prevalencia de los trastornos del ánimo comórbidos en sujetos con dependencia de sustancias, dando un vuelco en los supuestos previos acerca de que la depresión en estos pacientes era simplemente un artefacto de la intoxicación y/o de la abstinencia, y que por tanto no requería de tratamiento. Sin embargo, aun es limitada nuestra comprensión acerca de las relaciones bidireccionales entre los trastornos del ánimo y el abuso de sustancias en cuanto a los cursos y pronósticos de la enfermedad. Asimismo, llama la atención que existe poca investigación terapéutica para guiar la toma de decisiones clínicas cuando co-ocurren trastornos del ánimo y por uso de sustancias, dada su alta prevalencia y la carga para la salud pública. En este artículo se repasa lo que se sabe y los vacíos más destacados del conocimiento donde los datos podrían mejorar el diagnóstico y el tratamiento de estos pacientes complicados.

Évaluation et traitement des troubles de l'humeur dans le cadre de la toxicomanie

La reconnaissance et la prise en charge des troubles de l'humeur chez les personnes consommant de l'alcool et/ou d'autres substances sont des défis quotidiens pour les médecins, que ce soit dans le cadre hospitalier ou ambulatoire. Le diagnostic des troubles de l'humeur sous-jacents dans le contexte d'une toxicomanie existante nécessite un recueil soigneux des antécédents psychiatriques ; il est souvent déterminant pour une organisation et des résultats optimaux du traitement. Une absence de reconnaissance de la dépression majeure ou des troubles bipolaires chez ces patients peut entraîner une augmentation des taux de rechute, une récidive des troubles thymiques et un risque élevé de suicide réussi. Ces 10 dernières années, la recherche épidémiologique a clarifié la prévalence des troubles comorbides de l'humeur chez les personnes dépendantes d'une substance, infirmant les hypothèses antérieures considérant la dépression chez ces patients comme un simple artéfact de l'intoxication et/ou du sevrage, ne nécessitant donc aucun traitement. Cependant, notre compréhension des relations bidirectionnelles entre troubles de l'humeur et troubles de l'usage d'une substance en termes d'évolution de la maladie et de pronostic reste limitée. De même, le peu de recherche thérapeutique pour guider la décision clinique en cas de troubles concomitants de l'humeur et de l'usage de substances est marquant, compte tenu de leur haute prévalence et de leur poids dans la santé publique. Nous analysons ici ce qui est connu ainsi que les lacunes importantes dans nos connaissances dans ce domaine ; des résultats de recherche pourraient améliorer le diagnostic et le traitement de ces patients compliqués.

44. Himmelhoch JM, Mulla D, Neil JF, Detre TP, Kupfer DJ. Incidence and significance of mixed affective states in a bipolar population. *Arch Gen Psychiatry.* 1976;33:1062-1066.

45. Keller MB, Lavori PW, Coryell W, et al. Differential outcomes of pure manic, mixed/cycling, and pure depressive episodes in patients with bipolar illness. *JAMA*. 1986;255:3138-3142.

46. Goldberg JF, Garno JL, Leon AC, Kocsis J, Portera L. A history of substance abuse complicates remission from acute mania in bipolar disorder. *J Clin Psychiatry*. 1999;60:733-740.

47. Weiss RD, Ostacher MJ, Otto MW, et al. Does recovery from substance use disorder matter in patients with bipolar disorder? *J Clin Psychiatry*. 2005;66:730-735.

48. Curran GM, Sullivan G, Williams K, Han X, Allee E, Kotria KJ. The association of psychiatric comorbidity and use of the emergency department among persons with substance use disorders: an observational cohort study. *BMC Emergency Med*. 2008;8:17-23.

49. Sonne SC, Brady KT, Morton WA. Substance abuse and bipolar affective disorder. *J Nerv Ment Dis. 19*94;182:349-352.

50. Goldstein BI, Levitt AJ. Factors associated with temporal priority in comorbid bipolar I disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions. *J Clin Psychiatry*. 2006;67:643-649.

51. Himmelhoch JM, Garfinkel ME. Sources of lithium resistance in mixed mania. *Psychopharmacol Bull*. 1986;22:613-620.

52. Passmore MJ, Garnham J, Duffy A, et al. Phenotypic spectra of bipolar disorder in responders to lithium versus lamotrigine. *Bipolar Disord*. 2003;5:110-114.

53. Morrison JR. Bipolar affective disorder and alcoholism. *Am J Psychiatry*. 1974;131:1130-1133.

54. Swann AC, Dougherty DM, Pazzaglia PJ, Pham M, Steinberg JL, Moeller FG. Increased impulsivity associated with severity of suicide attempt history in patients with bipolar disorder. *Am J Psychiatry*. 2005;162:1680-1687.

55. Potash JB, Kane HS, Chiu Y, et al. Attempted suicide and alcoholism in bipolar disorder: clinical and familial relationships. *Am J Psychiatry*. 2000;157:2048-2050.

56. Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. *Bipolar Disord*. 2003;5:58-61.

57. Hawton K, Sutton L, Haw C, Sinclair J, Harriss L. Suicide and attempted suicide in bipolar disorder: a systematic review of risk factors. *J Clin Psychiatry*. 2005;66:693-704.

58. Oquendo MA, Currier D, Liu S-M, Hasin DS, Grant BF, Blanco C. Increased risk for suicidal behavior in comorbid bipolar disorder and alcohol use disorders: results from the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC). *J Clin Psychiatry*. 2010;71:902-909.

59. Yoon YH, Chen CM, Yi HE, Moss HB. Effect of comorbid alcohol and drug use disorders on premature death among unipolar and bipolar disorder decedents in the United States, 1999 to 2006. *Compr Psychiatry*. 2011;52:453-464.

60. DelBello MP, Hanseman D, Adler CM, et al. Twelve-month outcome of adolescents with bipolar disorder following first hospitalization for a manic or mixed episode. *Am J Psychiatry*. 2007;164:582-590.

61. Strakowski SM, Sax KW, McElroy SL, Keck PE, Hawkins JM, West SA. Course of psychiatric and substance abuse syndromes co-occurring with bipolar disorder after a first psychiatric hospitalization. *J Clin Psychiatry*. 1998;59:465-471.

62. Tohen M, Waternaux CM, Tsuang MT. Outcome in Mania: a 4-year prospective follow-up of 75 patients utilizing survival analysis. *Arch Gen Psychiatry*. 1990;47:1106-1111.

63. Tohen M, Waternaux CM, Tsuang MT. Four-year follow-up of twenty-four first episode manic patients. *J Affect Disord*. 1990;19:79-86.

64. Strakowski SM, DelBello MP, Fleck DE, et al. Effects of co-occurring alcohol abuse on the course of bipolar disorder following first hospitalization for mania. *Arch Gen Psychiatry*. 2005;62:851-858.

65. Drake RE, Xie H, McHugo GJ, Shumway M. Three-year outcomes of long-term patients with co-occurring bipolar and substance use disorders. *Biol Psychiatry*. 2004;56:749-756.

66. Farren CK, Murphy P, McElroy S. A 5-year follow-up of depressed and bipolar patients with alcohol use disorder in an Irish population. *Alcohol Clin Exp Res.* 2014;38:1049-1058.

67. Fleck DE, Arndt S, DelBello MP, Strakowski SM. Concurrent tracking of alcohol use and bipolar disorder symptoms. *Bipolar Disord*. 2006;8:338-344.

68. Baethge C, Hennen J, Khalsa H-MK, Salvatore P, Tohen M, Baldessarini RJ. Sequencing of substance use and affective morbidity in 166 first-episode bipolar I disorder patients. *Bipolar Disord*. 2008;10(6):738-741.

69. Jaffe WB, Griffin ML, Gallop R, et al. Depression precipitated by alcohol use in patients with co-occurring bipolar and substance use disorders. *J Clin Psychiatry*. 2009;70:171-176.

70. Prisciandaro JJ, Brown DG, Brady KT, Tolliver BK. Comorbid anxiety disorders and baseline medication regimens predict clinical outcomes in individuals with co-occurring bipolar disorder and alcohol dependence: results of a randomized controlled trial. *Psychiatry Res* 2011;188:361-365.

71. Prisciandaro JJ, DeSantis SM, Chiuzan C, Brown DG, Brady KT, Tolliver BK. Impact of depressive symptoms on future alcohol use in patients with co-occurring bipolar disorder and alcohol dependence: a prospective study. *Alcohol Clin Exp Res*. 2012;36:490-496.

72. Weiss RD, Griffin ML, Kolodziej ME, et al. A randomized trial of integrated group therapy versus group drug counseling for patients with bipolar disorder and substance dependence. *Am J Psychiatry*. 2007;164:100-107.

73. McDonell MG, Srebnik D, Angelo F, et al. Randomized controlled trial of contingency management for stimulant use in community mental health patients with serious mental illness. *Am J Psychiatry*. 2013;170:94-101.

74. Nunes EV, Levin FR. Treatment of depression in patients with alcohol or other drug dependence. A meta-analysis. *JAMA*. 2004;291:1887-1896.

75. Pettinati HM. Antidepressant treatment of co-occurring depression and alcohol dependence. *Biol Psychiatry*. 2004;56:785-792.

76. Kranzler HR, Mueller T, Cornelius J, et al. Sertraline treatment of co-occurring alcohol dependence and major depression. *J Clin Psychopharmacol*. 2006;26:13-20.

77. Pettinati HM, Oslin DW, Kampman KM, et al. A double-blind, placebo-controlled trial combining sertraline and naltrexone for treating co-occurring depression and alcohol dependence. *Am J Psychiatry*. 2010;167:668-675.

78. Moak DH, Anton RF, Latham PK, Voronin KE, Waid RL, Durazo-Arvizu R. Sertraline and cognitive behavioral therapy for depressed alcoholics: results of a placebo-controlled trial. *J Clin Psychopharmacol*. 2003;23(6):553-562.

79. Brown ES, Sunderajan P, Hu LT, Sowell SM, Carmody TJ. A randomized, double-blind, placebo-controlled trial of lamotrigine therapy in bipolar disorder, depressed or mixed phase and cocaine dependence. *Neuropsychopharmacology*. 2012;37:2347-2354.

80. Brown ES, Gorman AR, Hynan LS. A randomized, placebo-controlled trial of citicoline add-on therapy in outpatients with bipolar disorder and cocaine dependence. *J Clin Psychopharmacol*. 2007;27:498-502.

81. Brown ES, Gabrielson B. A randomized, double-blind, placebo-controlled trial of citicoline for bipolar and unipolar depression and methamphetamine dependence. *J Affect Disord*. 2012;143:257-260.

82. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind, placebo-controlled study. *Arch Gen Psychiatry*. 2005;62:37-45.

83. Brown ES, Garza M, Carmody TJ. A randomized, double-blind, placebo-controlled add-on trial of quetiapine in outpatients with bipolar disorder and alcohol use disorders. *J Clin Psychiatry*. 2008;69:701-705.

84. Stedman M, Pettinati HM, Brown ES, Kotz M, Calabrese JR, Raines S. A double-blind, placebo-controlled study with quetiapine as adjunct therapy with lithium or divalproex in bipolar I patients with coexisting alcohol dependence. *Alcohol Clin Exp Res*. 2010;34:1822-1831.

85. Brown ES, Davila D, Nakamura A, et al. A randomized, double-blind, placebo-controlled trial of quetiapine in patients with bipolar disorder, mixed or depressed phase, and alcohol dependence. *Alcohol Clin Exp Res*. 2014;38:2113-2118.

86. Brown ES, Carmody TJ, Schmitz JM, et al. A randomized, double-blind, placebo-controlled pilot study of naltrexone in outpatients with bipolar disorder and alcohol dependence. *Alcohol Clin Exp Res*. 2009;33:1863-1869.

87. Tolliver BK, DeSantis SM, Brown DG, Prisciandaro JJ, Brady KT. A randomized, double-blind, placebo-controlled clinical trial of acamprosate in alcohol-dependent individuals with bipolar disorder: a preliminary report. *Bipolar Disord*. 2012;14:54-63.

88. Bodkin AJ, Zornberg GL, Lukas SE, Cole JO. Buprenorphine treatment of refractory depression. *J Clin Psychopharmacol*. 1995;15:49-57.

89. Knudson HK, Abraham AJ, Roman PM. Adoption and implementation of medications in addiction treatment programs. *J Addict Med*. 2011;5:21-27.

90. Simon NM, Otto MW, Weiss RD, Bauer MS, Miyahara S, Wisniewski SR. Pharmacotherapy for bipolar disorder and comorbid conditions. Baseline data from STEP-BD. *J Clin Psychopharmacol*. 2004;24:512-520.

91. Diaz FJ, James D, Botts S, Maw L, Susce MT, de Leon J. Tobacco smoking behaviors in bipolar disorder: a comparison of the general population, schizophrenia, and major depression. *Bipolar Disord*. 2009;11(2):154-165.

92. Thorndike AN, Stafford RS, Rigotti NA. US physicians' treatment of smoking in outpatients with psychiatric diagnoses. *Nicotine Tobacco Res*. 2001;3(1):85-91.

93. Himelhoch S, Daumit G. To whom do psychiatrists offer smoking-cessation counseling? *Am J Psychiatry*. 2003;160(12):2228-2230.