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Abstract

Mood disorders, which include the depressive disorders and bipolar disorders, are prevalent in the general population and are among the most common disorders observed to co-occur with substance use disorders. Mood disorders have been associated with worse prognosis among substance-dependent patients. Further, treatment of co-occurring mood disorders has been shown to improve treatment outcome among substance-dependent patients with improvement in both mood and substance use. At the same time, mood symptoms and syndromes among substance-dependent patients frequently remit when the patient enters treatment for substance dependence and reduces substance use or achieves abstinence – no specific mood disorder treatment required. Thus, it is important for clinicians working with substance-abusing patients to be able to recognize mood disorders in the clinical history, distinguish mood disorders that require specific treatment, recommend appropriate treatment options, and monitor clinical course. This chapter reviews the evidence on the diagnosis and treatment of co-occurring substance and mood disorders, with emphasis on depressive disorders.

117.1 Introduction

The co-occurrence of mood and substance use disorders has been a source of considerable controversy, sparked by the complexity of potential relationships between mood syndromes and substance use. For example, in an alcoholic, do depressive symptoms represent side effects of chronic alcohol exposure that will resolve if the patient achieves abstinence? Or do they represent an independent mood disorder that requires specific treatment, either with behavioral therapy, medication, or a combination of the two? In any given patient, either of these explanations may be correct. Effective management of co-occurring mood symptoms in substance-abusing patients requires a nuanced awareness of the differential diagnosis of the mood symptoms. This chapter will attempt to provide a guideline for clinicians to the differential diagnosis and therapeutics of mood syndromes among substance-dependent patients, based on the current evidence.

The co-occurrence of bipolar disorders and substance use disorders is covered in detail in a separate chapter of this text. However, when conducting a diagnostic evaluation and treatment planning for patient with a substance use disorder and mood symptoms, it is very important to consider bipolar disorders in the differential diagnosis, since the treatment implications are quite different. This chapter therefore provides an overview of the diagnosis of bipolar disorders.

117.2 Prevalence and Co-occurrence

117.2.1 DSM-IV and DSM-5

The publication of this textbook coincides with the recent (May 2013) release of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) (American Psychiatric Association 2013). However, virtually all the empirical evidence that will be cited in this chapter, bearing on co-occurrence of mood and substance use disorders, derives from investigations that used DSM-IV (American Psychiatric Association 1994) or earlier criteria sets. The criteria for depressive disorders (major depression, persistent depressive disorder (dysthymia)) and bipolar disorders (bipolar I, bipolar II, cyclothymia) have changed little between DSM-IV and DSM-5. Dysthymia, which in DSM-IV described chronic low-grade depression, has been renamed persistent depressive disorder in DSM-5 and now encompasses both chronic low-grade depression and chronic major depression. DSM-5 added a new category of disruptive mood dysregulation disorder (DMDD) to the group of depressive disorders. DMDD is intended to distinguish children with predominantly irritable mood, but without other features of bipolar disorder, from children in the bipolar spectrum. The substance-induced diagnoses (substance-induced depressive disorder, substance-induced bipolar disorder) are similar conceptually in DSM-5 and DSM-IV with some subtle differences reviewed below.

A thorough review of the diagnostic criteria for depressive and bipolar disorders is beyond the scope of this chapter. Readers who are not familiar with these diagnostic criteria should review the DSM-5 (American Psychiatric Association 2013), which provides detailed descriptions.

The substance use disorders were changed in DSM-5, in that substance dependence (DSM-IV) and substance abuse (DSM-IV) have been combined into one category, named substance use disorder (DSM-5). This was done because the weight of the evidence indicated the criteria for DSM-IV substance abuse, which involved hazardous use (e.g., driving while intoxicated), social or interpersonal problems related to use, or failure to perform in major role responsibilities, were intermixed across the severity spectrum with substance dependence criteria, representing part of a chronic pattern of substance use with loss of control, tolerance, dependence, and adverse consequences (Hasin et al. 2013). Another difference between DSM-IV and DSM-5 is the addition of “craving” as a criterion for substance use disorder in DSM-5. In terms of the evidence on the co-occurrence of mood and substance use disorders, these change should make little difference, since the three retained abuse criteria and craving are unidimensional with the seven dependence criteria (all therefore indicating the same underlying condition) and most epidemiological and treatment research on the comorbidity of depression and substance disorders concerned co-occurrence with substance dependence. Further, substance dependence (DSM-IV) and substance use disorder

(DSM-5) are conceptually similar, representing a chronic pattern of substance use with loss of control, tolerance, dependence, and adverse consequences.

In summary, the DSM-5 criteria sets for mood and substance use disorders are similar enough to DSM-IV, and prior criteria that the evidence on co-occurrence described in this chapter can be expected to generalize to the DSM-5 framework. Future research examining co-occurrence of substance and other mental disorders in the DSM-5 framework is needed. Meanwhile in this chapter, evidence described on prevalence and treatment will be derived from studies based on DSM-IV or earlier criteria sets.

117.2.2 Depressive Disorders

117.2.2.1 Major Depressive Disorder

Major depressive disorder represents an episode, lasting 2 weeks or more, of relatively severe depression, characterized by a persistent state, “most of the day, nearly every day” (American Psychiatric Association 2013), of either depressed mood or markedly diminished interest or pleasure in usual activities, or both, along with at least three or four associated symptoms, again occurring nearly every day (anorexia and weight loss, insomnia or hypersomnia, psychomotor agitation or retardation, fatigue or low energy, feelings of worthlessness or guilt, trouble concentrating or making decisions, recurrent thoughts of death or suicide). Major depression may occur as a single episode, but in patients, a chronic course is not uncommon, in which there are recurrent major depressive episodes, followed by partial remissions during which some of the depressive symptoms persist.

117.2.2.2 Persistent Depressive Disorder

Persistent depressive disorder (DSM-5), which was called *dysthymia* in DSM-IV, represents a chronic syndrome of depressed mood “more days than not... for at least 2 years” (American Psychiatric Association 2013), along with at least 2 of the following associated symptoms – either low appetite or overeating, insomnia or hypersomnia, fatigue or low energy, low self-esteem, poor concentration or difficulty making decisions, and feelings of hopelessness. Persistent depressive disorder may be specified “with persistent major depression” or “with intermittent major depressive episodes” to indicate the confluence of major depressive episodes with the chronic low-grade symptoms.

117.2.2.3 Prevalence and Co-occurrence of Depressive Disorders with Substance Use Disorders

Like substance use disorders, depressive disorders are among the most commonly occurring mental disorders. Community surveys indicate 10 % or more of individuals have experienced a depressive disorder during their lifetime (Hasin et al. 2005). Depressive disorders are responsible for substantial suffering, functional impairment, lost productivity, and suicide risk. Large community surveys, such as the Epidemiological Catchment Area study (ECA) (Regier et al. 1990), the National Comorbidity

Survey (NCS) (Kessler et al. 1994; Kessler 1995), and the National Epidemiologic Survey on Alcoholism and Related Conditions (NESARC) (Hasin et al. 2005; Grant et al. 2005), consistently show that the presence of a depressive disorder significantly increases the risk of alcohol or drug dependence (or vice versa) by a factor of 2 or more. Treatment-seeking samples tend to display even greater comorbidity due to the relatively greater severity of illness of treatment seekers. Across numerous studies of such samples, the prevalence of major depression has ranged from 15 % to 50 %, making it probably the most common co-occurring psychiatric disorder encountered among drug- or alcohol-dependent patients in treatment (Hasin et al. 2004).

117.2.2.4 Prognostic Effects of Depressive Disorders on Substance Use Disorders

Many longitudinal studies have found that the presence of depression in drug- or alcohol-dependent patients is associated with worse treatment outcome and prognosis. These findings suggest the importance of identifying and treating depression among substance-dependent patients, since the implication is that treatment of the depression has the potential to improve prognosis. Importantly, the findings of the adverse prognosis of depression are most consistent among studies where a depressive disorder (mainly major depression) is diagnosed by clinical history and structured diagnostic assessment. Findings on the association between depression and prognosis of substance use are less consistent when depression is measured only with cross-sectional scales (Hasin et al. 2004). For example, one study that followed alcohol-dependent patients for a year after an index hospitalization found that a diagnosis of major depression was associated with poor drinking outcome over the coming year, while the Hamilton Depression Rating Scale score at baseline was not (Greenfield et al. 1998).

117.2.3 Bipolar Disorders

Bipolar disorders are more rare in the general population, but are more strongly associated with co-occurring substance use disorders. Large community surveys yield estimates of the lifetime prevalence of bipolar I disorder ranging from 1 % to 3 %, another 1 % for bipolar II disorder, and 2 % or more having subthreshold disorders in the bipolar spectrum (Grant et al. 2005; Merikangas et al. 2007). Although bipolar disorders are characterized by the presence of manic or hypomanic episodes during the lifetime, these episodes alternate with episodes of major depression or chronic depression, and the depressed periods typically predominate, particularly later in the course of the illness. Thus, bipolar patients are most likely to present clinically as depressed. When evaluating a depressed, substance-using patient, it is therefore very important to search the history for evidence of past manic or hypomanic episodes because the treatment of bipolar disorders differs significantly from the treatment of depressive disorders. The cornerstone of the treatment of bipolar disorder is mood stabilizer medications – lithium, anticonvulsants, or neuroleptics. Treating bipolar depression with antidepressant medications alone can be ineffective or even cause worsening of mood instability.

117.2.3.1 Bipolar I Disorder

Bipolar I disorder is characterized by the presence of one or more manic episodes over course of the lifetime. Manic episodes are characterized by a week or more of persistently elevated, expansive, or irritable mood, accompanied by at least three associated symptoms, including grandiose thinking, decreased need for sleep, increased talkativeness, racing thoughts, distractibility, increased activity level, and risky or foolish behavior that the person would not usually engage in. The syndrome is severe and causes marked impairment in functioning. Mania may become psychotic with paranoid or grandiose delusions (e.g., a patient becomes convinced that he/she is a messiah or on a special mission from God). Typically, the course of bipolar I includes episodes of major depression, may also include hypomanic episodes, and typically runs a course that is predominated by depressive symptoms.

117.2.3.2 Bipolar II Disorder

Bipolar II disorder is characterized by one or more hypomanic (as opposed to manic) episodes, along with one or more episodes of major depression over the lifetime. A hypomanic episode resembles a manic episode, except that hypomania may be shorter, and is less severe. There must be a change in functioning to meet criteria for hypomania, but hypomania does not cause marked impairment or psychosis. Again, bipolar II frequently runs a predominantly depressive course.

117.2.3.3 Co-occurrence of Bipolar and Substance Use Disorders and Prognostic Effects

Large-scale community surveys indicate that the presence of a bipolar disorder increases the odds of having an alcohol use disorder by a factor of 5 or more and a drug use disorder by a factor of 8 or more (Regier et al. 1990; Kessler et al. 1994; Kessler 1995; Hasin et al. 2005; Grant et al. 2005). In outpatients seeking treatment for substance use disorders, bipolar disorder is less commonly encountered than depressive disorders because bipolar is less frequent in the general population. However, patients with co-occurring bipolar and substance use disorders are particularly likely to be encountered in inpatient settings dealing with more severe dually diagnosed patients.

The co-occurrence of bipolar and substance use disorders is associated with worse outcome for both disorders. Patients with bipolar disorders can be very difficult to manage until the disorder is recognized and successfully treated with mood stabilizers. Conversely, finding the right mood stabilizer regimen for a given patient can be dramatically effective. This, again, suggests the importance, when evaluating substance-dependent patients, of taking a careful past history for past episodes of mania or hypomania.

117.2.4 Co-occurring Depression and Substance Use as a Signal for Other Disorders

A recent analysis of the NESARC data on co-occurrence of mood and substance use disorders yielded an interesting finding (Hasin et al. 2007). When the

association between major depression and substance use disorders is analyzed in such a way as to control for the presence of other disorders (bipolar disorder, anxiety disorders, etc.), the odds ratio of association between depression and substance use disorders is substantially reduced. This suggests that the apparent association between depression and substance use disorders may be explained, at least in part by the presence of the other co-occurring disorders, including anxiety disorders, since anxiety is a commonly occurring symptom among those with depression. In contrast, the association between bipolar disorder and substance use disorders remained significant after controlling for the other disorders. Substance use disorders have high rates of co-occurrence with anxiety disorders, such as panic disorder, social anxiety disorder, and post-traumatic stress disorder (PTSD); attention deficit hyperactivity disorder (ADHD); and personality disorders, including antisocial personality and borderline personality. Each of these disorders, in turn, has high co-occurrence with depressive disorders or symptoms or has symptoms that resemble depression. Thus, in substance-dependent patients, depressive symptoms may be a signal that other disorders are also present. It is therefore important to take a careful history looking, not only for bipolar disorder but also for anxiety disorders, ADHD, or personality disorders. These disorders also have distinct behavioral and pharmacological treatment indications, and instituting appropriate treatment will be important to securing the best clinical outcome.

117.3 Diagnosis of Co-occurring Mood Disorders with Substance Use Disorders

In approaching the differential diagnosis of a patient with a substance use disorder and mood symptoms, it is important to recognize that there are multiple potential relationships between mood symptoms and a substance use disorder. There may be an independent mood disorder (e.g., major depressive disorder or bipolar disorder), or the depressive symptoms may be a manifestation of another co-occurring disorder such as PTSD or ADHD. Mood and substance use disorders may be related by common genetic or environmental risk factors. Stress is the most obvious example of this, as stress is a causal risk factor for both mood disorders and substance use disorders.

Perhaps most commonly, substance use causes mood symptoms, either as part of substance intoxication or withdrawal or as a result of the toxic effects of chronic exposure to substances. Moreover, individuals with substance use disorders often experience negative consequences and losses (e.g., medical problems, loss of employment or family), which may trigger depressive symptoms. Some of these substance-related or substance-induced mood symptoms will resolve if the patient is able to achieve abstinence. Hence, it is almost always appropriate to initiate treatment for a substance use disorder, while sorting out the co-occurring mood disorder. If the patient's substance use is substantially reduced or resolved, the mood symptoms may resolve with it. A number of studies across alcohol- and

drug-dependent samples have shown that initiation of treatment for substance use disorders and achievement of abstinence are associated with marked improvement in mood symptoms (Brown and Schuckit 1988; Weddington et al. 1990; Strain et al. 1991; Satel et al. 1991; Brown et al. 1995; Liappas et al. 2002).

It is also important to bear in mind that resolution of a depressive syndrome with treatment of the substance abuse alone is not pathognomonic of a substance-induced depression. Depressive disorders, particularly in the mild to moderate range of severity, respond well to psychotherapy, such as cognitive behavioral therapy (CBT) or interpersonal therapy (IPT). Treatment for substance use disorders generally includes nonspecific psychotherapeutic elements, such as development of a supportive clinician-patient relationship and treatment alliance, which are likely to be helpful with treating depression. Further, many treatments for substance use disorders include components on coping with stress and with dysphoric moods that are quite similar to cognitive behavioral techniques for treating mood and anxiety disorders. Further, reductions in substance abuse and related problems in response to treatment are likely to reduce stress and improve self-efficacy, also likely to help depression. In summary, good treatment for substance use disorders may also be effective for treatment of an independent depressive disorder.

117.3.1 DSM-IV/DSM-5 Approach to Co-occurring Mood and Substance Use Disorders

Before the advent of DSM-IV, there was not a clear consensus on how to diagnose co-occurring mood disorders in the setting of substance use disorders. There was recognition that some co-occurring mood disorders were independent of substance use and some mood syndromes were caused by substance use, which would resolve once abstinence was achieved. However, determining the optimal way to handle the large proportion of cases, in which the history is not so clear with respect to relative onset and offset, is less obvious, especially when the patient does not quickly achieve abstinence. DSM-IV advanced the field by distinguishing between independent mood disorders, substance-induced mood disorders, and mood symptoms that are usual effects of substances and for providing some criteria to make the distinctions. DSM-5 has retained this system. Substance-induced mood disorder provides a category in which to place the unclear cases, in which a mood disorder syndrome exceeds the symptoms that would be expected from intoxication and withdrawal, but the syndrome has not occurred in the absence of regular substance use. It has generated meaningful research as to its prognosis and course, as reviewed below.

117.3.1.1 Independent Mood Disorder

An independent mood disorder is diagnosed if the patient meets full criteria for the mood disorder (e.g., major depression, persistent depressive disorder, bipolar I) and the symptoms can be established by history to be temporally independent of substance abuse (prior onset or emergence or persistence during periods of

abstinence). DSM-IV also suggested that an independent disorder could be diagnosed if its symptoms were substantially in excess of effects expected to be caused by the substance(s) the patient was taking. DSM-5 deals with this by specifying that a substance-induced disorder is only diagnosed if the mood syndrome and symptoms are consistent with symptoms known to be caused by the substance(s). The clinical implications are similar. In the criteria sets for substance-induced mood disorders, DSM-5 suggests that a mood syndrome co-occurring with substance use may be considered an independent disorder (and thus distinguished from substance-induced disorder) if the mood syndrome had its onset prior to the onset of substance abuse, or persists for about 1 month or more after abstinence is achieved, or there is a clear past history of independent mood disorder episodes. An example might be a current major depression syndrome that had its onset concurrent with substance abuse in the current episode, but there is a clear history of one or more major depressive episodes during past abstinent periods.

117.3.1.2 Substance-Induced Mood Disorder

A substance-induced mood disorder is diagnosed if there is a “persistent disturbance in mood,” which (a) develops at or soon after substance intoxication or withdrawal and (b) the substance(s) in question is “capable of producing the symptoms,” and the syndrome is not better explained by a diagnosis of an independent mood disorder. There must be significant distress or impairment. Further, with respect to distinguishing a substance-induced mood disorder from usual effects of substances, the DSM-5 criteria state that a substance-induced mood disorder should be diagnosed, instead of a diagnosis of substance intoxication or withdrawal, only if “the mood symptoms predominate and are sufficiently severe to warrant clinical attention.” DSM-IV worded this slightly differently, indicating that substance-induced mood disorder should be diagnosed when the mood and related symptoms (e.g., insomnia) exceed what would be the expected effects of intoxication or withdrawal and warrant clinical attention. Again, the clinical implications are similar.

117.3.1.3 Usual Effects of Substances

Mood symptoms, such as depressed mood, insomnia, and weight loss, can also be usual effects of substance intoxication or withdrawal. DSM-IV and DSM-V contain detailed criteria sets for the intoxication and withdrawal syndromes of alcohol, nicotine, and each of the other commonly abused drugs. Clinicians should be mindful of these lists of symptoms when evaluating patients with co-occurring mood symptoms and substance use. These symptoms have various time frames, but generally, symptoms of intoxication last only for the few hours during and after substance ingestion while blood levels are peaking and before they substantially decrease. Symptoms of withdrawal usually evolve and resolve over a period of a few days. Subacute withdrawal syndromes (also called protracted withdrawal), sometimes lasting a few weeks, have been described, particularly for alcohol and opioid dependence, although boundaries between this phenomenon and substance-induced disorders can be difficult to define.

Depressed mood and related symptoms (e.g., anxiety, fatigue, hypersomnia, insomnia, difficulty concentrating, irritability) occur variously as part of the withdrawal syndromes of most of the common addictive substances. In summary, when conducting a diagnostic evaluation on a substance-using patient, familiarity with the intoxication and withdrawal effects of the substance(s) involved is important in order to distinguish mood symptoms that are best explained as components of intoxication or withdrawal from symptoms that are better explained as a substance-induced disorder.

117.3.1.4 Co-occurring Bipolar and Substance Use Disorder

Episodes of frank mania are generally too persistent (1 week or more) and too severe to be explained as substance induced. For example, cocaine or methamphetamine intoxication may produce a syndrome closely resembling mania (increased activity, hyper-loquaciousness, grandiosity, lack of need for sleep, and psychosis with paranoid or grandiose delusions), but this typically only lasts for the duration of the drug binge, a day at most, after which there will be a crash with the typical depressive withdrawal symptoms (fatigue, hypersomnia, depressed mood, etc.). Hence, a history of one or more episodes of frank mania in a patient presenting with co-occurring mood symptoms and substance problems is clear evidence of co-occurring independent bipolar disorder that requires appropriate mood stabilizer medication.

Hypomania can be more difficult to identify both in the present and historically. Hypomania is milder, and patients may not report it because they do not remember it or did not experience it as a departure from normal functioning. Moreover, periods of elevated mood, and increased energy and activity, may be difficult to distinguish from periods of normal mood – for example, when a chronically depressed patient becomes euthymic or when a patient has an exciting life event such as a new job or another major success. Periods of hypomania can be difficult to distinguish in a patient with heavy stimulant use, given the shorter duration of hypomania and the overlap in symptoms between hypomania and cocaine or stimulant intoxication (e.g., euphoria, increased sociability). As with depressive disorders, to confirm an independent bipolar II disorder, it becomes important to seek episodes in the history in which syndromes of hypomania occurred in the absence of stimulant-like substances.

117.3.2 Course and Prognosis of DSM-IV Independent and Substance-Induced Depression

Prior to DSM-IV, considerable evidence existed that independent depressive disorders could be identified with distinct prognostic and treatment implications. Brown and Schuckit showed among hospitalized alcoholics that a history of major depression prior to the onset of alcohol problems over the patient's lifetime (primary depression) was associated with depressive symptoms that persisted despite 3–4 weeks of abstinence (Brown and Schuckit 1988; Brown et al. 1995).

Rounsaville and colleagues, using the Schedule for Affective Disorder and Schizophrenia, a structured diagnostic instrument, found major depression to be associated with worse prognosis among drug-dependent patients (Rounsaville et al. 1982, 1986; Carroll et al. 1993). We and others found that depression with evidence of temporal independence from substance use either by history (Nunes et al. 1993, 1998; McGrath et al. 1996) or through observed persistence of depression symptoms during abstinence (Mason et al. 1996; Cornelius et al. 1997; Roy 1998) responded to antidepressant medication.

117.3.2.1 Structured Diagnostic Assessment

With the advent of DSM-IV, the Structured Clinical Interview for DSM-IV (SCID) incorporated a module for substance-induced mood disorder and logic for diagnosing a mood syndrome as independent or substance induced. However, the determinations were left largely up to clinical judgment with little guidance in the interview as to how to make the distinction. The Psychiatric Research Interview for Substance and Mental Disorders (PRISM) (Hasin et al. 2006) was developed to operationalize the diagnosis of co-occurring substance and other mental disorders within the DSM-IV framework. For a given syndrome, such as major depression, the interviewer is asked, for each criterion symptom, to judge whether that symptom appears attributable to usual effects of substances. The substances that might cause that symptom, either as intoxication or withdrawal effects, are listed. For example, when a depressed patient reports insomnia, the interviewer is asked to determine whether substances that might cause insomnia (stimulant intoxication or alcohol, sedative, or opioid withdrawal) could explain the insomnia. The insomnia is only scored as positive, and allowed to contribute to a diagnosis of a depressive disorder, if it can be determined either not related to or exceeding the expected effects of the substances the patient is taking. If sufficient criteria are endorsed to allow diagnosis of a depressive syndrome, then the interviewer is asked to determine whether the depressive syndrome is temporally independent of current substance use in terms of its onset and persistence during abstinence. If the history indicates that the depressive episode started prior to the onset of substance use or persists during a substantial abstinent period (e.g., a month or more), then it is diagnosed as independent. Otherwise, it is diagnosed as substance induced.

Thus, the PRISM provides an operationalized definition of substance-induced depression that is quite stringent. It requires criteria for a full depressive syndrome (e.g., for major depression) to be met, and it requires that the symptoms contributing to that syndrome not be better explained as toxic or withdrawal effects. In contrast, DSM-IV criteria for substance-induced depression refer only to a syndrome of depression without specifying how many or which symptoms of depression need to be present. DSM-5 criteria for substance-induced depression similarly require that there be a persistent disturbance in mood or loss of interest (much like the essential two criteria for major depression) but no specific associated features (such as insomnia, fatigue, suicidal ideation). This highlights an area of vagueness in the DSM-IV and DSM-5 definitions of substance-induced disorders, which the PRISM sought to correct by being more definitive. The PRISM yields

a diagnosis of substance-induced major depression, rather than the more broad and vague category of substance-induced depression.

117.3.2.2 Prognostic Effects

Subsequent research with the PRISM established good to excellent reliability of diagnoses of independent and substance-induced major depression (Hasin et al. 2006). Further, there were clear prognostic effects. In a longitudinal study, substance-dependent patients entering an inpatient treatment facility were diagnosed with the PRISM while hospitalized, then followed for 1 year after discharge. Substance-induced major depression was found to predict failure to achieve abstinence after discharge from hospital, while independent major depression was found to predict relapse to substance use after periods of abstinence (Hasin et al. 2002; Samet et al. 2013). Both independent and substance-induced depression were associated with suicidal ideation (Aharonovich et al. 2002). Further, over half of cases diagnosed as substance-induced depression at baseline converted into an independent depression over the year's follow-up, based on the major depression persisting during a period of at least a month of abstinence (Nunes et al. 2006). Predictors of conversion to independent depression included a past history of an independent major depression and either PTSD or borderline personality disorder (Nunes et al. 2006), again suggesting the importance of identifying other disorders that commonly co-occur with both mood and substance use disorders. Studies with other samples and diagnostic methods have similarly suggested the validity and prognostic significance of independent and substance-induced depressive disorders as conceptualized by DSM-IV/DSM-5 (Schuckit et al. 1997; Ries et al. 2001, 2008) and the finding that a substantial proportion of substance-induced depression will convert to an independent depressive disorder over time (Ramsey et al. 2004).

117.3.2.3 A Note About Terminology

The term "substance-induced depression" carries a causal implication, namely, that the substances are definitely causing the observed depression syndrome. This can cause clinicians to underestimate the potential clinical significance of a substance-induced depression, both because intoxication and withdrawal effects are also induced by substances and also because, as reviewed above, some depressions diagnosed as "substance induced" will turn out to be independent depressions if followed into a period of abstinence. Substance induced is to some extent a holding category for depressions for which the status as independent is uncertain at the time of diagnosis. It might be useful for clinicians to think of this as "substance induced until proven otherwise," to emphasize that continued clinical attention is warranted and that the depression may turn out to be independent or to warrant specific treatment.

In summary, these studies suggest that in diagnosing a substance-induced depression, it is important to determine what depressive syndrome is being observed – e.g., substance-induced major depression. The findings suggest that substance-induced depression is a valid and useful category. It represents a diagnostic entity that lies between usual toxic effects of substances and an

independent mood disorder. As the DSM-IV and DSM-5 criteria suggest, substance-induced depression “warrants clinical attention” because it carries adverse prognostic effects (suicidal ideation, lower likelihood of achieving abstinence) and is likely to convert to an independent depression over time. Further, as the DSM-5 criteria suggest, a past history of independent depression may be considered sufficient evidence to diagnose a current depression as independent, rather than substance induced. Other co-occurring disorders such as PTSD should also be suspected.

117.3.3 Summary and Recommendations for Diagnostic Assessment

117.3.3.1 Screening Instruments

Instruments that assess cross-sectional mood symptoms (e.g., Beck Depression Inventory, Hamilton Depression Rating Scale, Brief Symptom Inventory, or Quick Inventory of Depressive Symptomatology – Self-Report (QIDS-SR)) are useful for screening. However, by themselves they do not indicate the presence of any specific mood disorder and have unclear prognostic or treatment implications.

117.3.3.2 Clinical History and DSM-IV/DSM-5 Criteria

A substance-dependent patient with mood symptoms should be evaluated by taking a careful lifetime clinical history. The history should seek to establish the onset of substance use disorders over the lifetime and substantial periods of abstinence lasting a month or more. The history should then establish the onset and course of mood syndromes (major depressive episodes, persistent depressive disorder, mania, hypomania), in the context of the lifetime course of substance use, and apply the DSM-5 criteria for independent or substance-induced disorders. Among other things, this means establishing that symptoms of a mood disorder are not better explained as usual effects of substances or exceed what would be expected from the usual effects of substances. A mood disorder that cannot be established to be temporally independent of substance abuse, but exceeds the expected effects of substances, is diagnosed as substance induced. For substance-induced syndromes, we also recommend noting the full syndrome that is in evidence, for example, “substance-induced major depression” if the full criteria for major depression are met (i.e., five or more criteria are met), as some of the stronger prognostic data pertain to substance-induced depression defined in this way (Hasin et al. 2002; Aharonovich et al. 2002; Nunes et al. 2006; Samet et al. 2013).

117.3.3.3 Search the History for Mania or Hypomania

The presence of one or more episodes of mania and hypomania indicates a bipolar disorder, which carries prognostic and treatment implications distinct from depression. Mania and hypomania may be difficult to elicit in the history. It is often helpful to interview family members, who may recall such episodes when the patient does not.

117.3.3.4 Look for Other Co-occurring Disorders

We also recommend a thorough review of the history for other disorders that commonly co-occur with mood disorders, including PTSD, social anxiety disorder, and other anxiety disorders; ADHD; and borderline personality. The presence of mood symptoms may signal the presence of one of these disorders. Such disorders have symptom patterns that are distinct from typical substance effects – substance use does not cause phobias, social anxiety, or reexperiencing symptoms of PTSD. Some have clear childhood onset (e.g., ADHD, social anxiety disorder), well prior to the onset of substance problems. And they have distinct treatment indications for both behavioral therapy and medications.

117.4 Treatment of Co-occurring Mood Disorders

117.4.1 Depressive Disorders

117.4.1.1 Antidepressant Medications

A number of placebo-controlled trials have examined the effect of antidepressant medication on mood and substance use outcome among substance-dependent patients with diagnosed mood disorders. Two meta-analyses (Nunes and Levin 2004; Torrens et al. 2005), published 10 years ago, reached similar conclusions, namely, that antidepressant medications are useful in improving both mood outcome and substance use outcome; these findings are more clear among alcohol-dependent patients. Among drug-dependent patients, there are fewer studies with less clear results. More recent studies have been mixed, with some negative trials (Gual et al. 2003; Kranzler et al. 2006; Cornelius et al. 2009; Raby et al. 2014). These include a large trial among alcohol-dependent outpatients that showed a high placebo response rate and no medication effect on mood or substance use outcome, despite patients being diagnosed with independent major depression using the PRISM. Other more recent trials have also been positive, at least in showing a beneficial effect of antidepressant medication on mood outcome (Hernandez-Avila et al. 2004; McDowell et al. 2005; Riggs et al. 2007).

117.4.1.2 Placebo Response and Other Factors Associated with Response to Antidepressants

A striking finding from the antidepressant trials is the wide variation in placebo response among studies, which varies from 20 % to more than 70 %, and the strong relationship between placebo response and study outcome. Studies with low placebo response tended to show beneficial effects of antidepressant medication on mood and substance use outcome, while studies with high placebo response showed no benefits of medication, a pattern observed in the original meta-analysis (Nunes and Levin 2004) and evident in the more recent studies (Gual et al. 2003; Kranzler et al. 2006; Cornelius et al. 2009; Raby et al. 2014; Hernandez-Avila et al. 2004; McDowell et al. 2005; Riggs et al. 2007). Several other study features were also found to be related to low placebo response and to benefit of medication, including

Table 117.1 Factors associated with low placebo response and beneficial effect of antidepressant medication in placebo-controlled trials among depressed, substance-dependent patients

Factor associated with low placebo response and medication efficacy	Potential mechanism	Implications for clinical management
Abstinence established before diagnosing depression	Withdrawal effects and substance-induced depression resolve with abstinence, leaving independent depressions more likely to benefit from medication	Initiate treatment with hospitalization for severely ill patients or evidence-based psychosocial treatment (e.g., cognitive behavioral relapse prevention). Some depression will resolve. Depression that persists should be considered for antidepressant medication
Diagnosis of a depressive disorder, rather than merely depressive symptoms	Depressive symptoms are more likely to represent withdrawal effects or be substance induced	Base diagnosis of depression on careful clinical history and application of DSM-IV/DSM-5 criteria for independent or substance-induced depression
Noradrenergic or mixed-mechanism antidepressants	Less evidence of efficacy for serotonin reuptake inhibitors (SRI) among substance-dependent patients may relate to the study samples (high placebo response) rather than lack of efficacy. However, several trials suggest SRI makes drinking worse among early onset alcoholics	SRIs may still be considered the first-line treatment based on their good safety and tolerability, but consider switching to a noradrenergic or mixed-mechanism medication (e.g., venlafaxine, duloxetine, mirtazapine, nefazodone) if non-responsive to SRI
Concurrent manual-guided behavioral intervention	Behavioral interventions for substance use disorders (e.g., cognitive behavioral relapse prevention) typically contain elements likely to help with depression (e.g., support, coping skills)	Initiate psychosocial treatment for the substance use disorder as a first step

(a) diagnosis of depression after abstinence has been established, particularly enforced abstinence on an inpatient unit; (b) diagnosis of a depressive disorder, as opposed to merely depressive symptoms; (c) noradrenergic or mixed-mechanism antidepressants (serotonin reuptake inhibitors have shown little evidence of efficacy); and (d) concurrent manual-guided psychosocial intervention (psychosocial interventions were associated with high placebo response and absence of benefit of medication). These are described further in Table 117.1 along with their possible mechanisms and implications for clinical practice.

The phenomenon of high placebo response is not surprising, given the evidence from the wider literature on treatment of depression, which shows cognitive

behavioral and other psychosocial interventions to be effective and shows high placebo response, particularly among patients with only mild to moderate depressive symptoms. Generally, the level of severity of depression in clinical trials needs to be high (severe) before there is consistent evidence that antidepressant medication is superior to placebo (Fournier et al. 2010). For the treatment of substance-dependent patients with depression, then, a reasonable first step is to initiate treatment for the substance use disorder. For more severely depressed or substance-dependent patients, hospitalization may be needed to induce abstinence. Or, on an outpatient basis, evidence-based behavioral treatment for the addiction can be offered. If the depression fails to respond once addiction treatment is initiated, then specific antidepressant treatment should be considered.

117.4.1.3 Behavioral Treatments

As noted above, manual-guided psychosocial treatments for substance use disorders are associated with high placebo response rates in the antidepressant medication trials, suggesting these interventions have some efficacy at treating depression in this population. Some controlled trials have examined cognitive behavioral treatments for depression among substance-dependent patients, with some evidence of efficacy (Brown et al. 1997, 2001; Patten et al. 1998; Carpenter et al. 2006, 2008; Daughters et al. 2008; Hides et al. 2010). Psychosocial and behavioral treatments have solid evidence of efficacy for treatment of mood and anxiety disorders, and their use avoids risks of drug interactions that may be of concern when prescribing antidepressant medications to substance-dependent patients. Thus, such behavioral interventions may be considered as a first step, prior to medication, particularly when the severity of depression is in the mild to moderate range.

117.4.1.4 Treatment of the Substance Use Disorder

Again, it bears emphasizing that when a patient presents with combined substance use and mood disorders, treatment should begin by identifying the substance as problem and initiating treatment for the substance use disorder. This could range from brief motivational intervention to a more formal treatment regimen. Successful treatment of the substance use disorder, with resultant reduction in substance use or abstinence, eliminates the toxic effects the substance may likely be having on the nervous system and is likely to improve or even eliminate symptoms of depression (Brown and Schuckit 1988; Weddington et al. 1990; Strain et al. 1991; Satel et al. 1991; Brown et al. 1995; Liappas et al. 2002). That said, when a depressive disorder persists after initiation of treatment for the addiction, specific antidepressant treatment, either behavioral, medication, or a combination of the two, should be initiated.

117.4.1.5 Combined Medications for Depression and Substance Use

There have been a few studies of medications for treatment of addictions, such as disulfiram and naltrexone (Petrakis et al. 2005, 2007), buprenorphine, or methadone (Strain et al. 1991; Nunes et al. 1998), among patients with substance and mood or

anxiety disorders or symptoms. These studies suggest such medications are at least well tolerated and potentially effective at improving mood symptoms, probably because they are effective in reducing or eliminating substance use.

One innovative study examined the combination of sertraline and naltrexone for alcohol-dependent patients with depression, finding the combination superior to either medication alone or placebo (Pettinati et al. 2010). Medications for treating substance use disorders are generally underutilized and should be always considered as part of treatment planning generally, as well as specific treatment planning for patients with combined mood and substance use disorders.

117.4.2 Bipolar Disorders

Thorough reviews of medication treatments of bipolar disorder can be found in published reviews elsewhere (Suppes et al. 2005; Thase 2007), and treatment of bipolar disorders in the setting of substance use disorders is covered in detail in a separate chapter of this text. Briefly, lithium, anticonvulsants (e.g., valproate, carbamazepine, lamotrigine), and neuroleptics (particularly second-generation agents such as quetiapine, risperidone, and aripiprazole) are the mainstays of treatment for bipolar disorder. Among these, lithium (Geller et al. 1998) and valproate (Salloum et al. 2005) have been tested in controlled trials and found effective for patients with co-occurring bipolar and substance use disorders. Despite the typical predominance of depressive symptoms and syndromes among bipolar patients, antidepressant medications are often ineffective or even counterproductive among bipolar patients. This again highlights the importance of making the differential diagnosis between bipolar and depressive disorders with the clinical history.

Behavioral treatments can also be helpful as adjuncts to medication treatment for bipolar disorder by building treatment alliance, medication adherence, and coping skills (Craighead and Miklowitz 2000; Scott and Gutierrez 2004). Weiss and colleagues have developed a group behavioral treatment for patients with combined bipolar and substance use disorders, integrated group therapy (IGT), which has shown evidence of efficacy in a series of controlled trials (Weiss 2004; Weiss et al. 2007, 2009; Weiss and Connery 2011). Interestingly, among its key features, IGT encourages patients to think of their combined mood and substance problems as a single disorder (“bipolar substance abuse”). This stands in contrast to the DSM approach, reviewed above, which involves establishing separate mood and substance use disorder diagnoses. It suggests that a co-occurring mood and substance use disorder may be more than the sum of the separate diagnoses and best treated in an integrated fashion.

117.5 Conclusion

As we hope this chapter has illustrated, considerable evidence has accumulated that mood disorders can be distinguished from substance-related syndromes and

effectively treated, through a careful clinical history, and longitudinal observation of the response of mood symptoms and substance use as treatment is implemented. A guideline exists for the differential diagnosis of independent versus substance-induced mood disorders versus intoxication or withdrawal effects of substances, based on DSM-IV/DSM-5 criteria. In all cases, it makes sense to initiate treatment of the substance use disorder as a first step. Substance-induced depression, and even cases that meet criteria for an independent depressive disorder, may respond to behavioral treatment for the substance use disorder. However, for cases that do not respond, specific antidepressant treatment should be considered – either medication or behavioral treatment or both. It has been shown that many cases of substance-induced depression, particularly if a full major depressive syndrome is present, will be observed to persist during abstinence over follow-up, thus converting to independent depression. For clear-cut or severe cases of major depression, initiation of antidepressant treatment may be considered concurrent with substance abuse treatment from the outset. A careful search of the history should be conducted for episodes of mania or hypomania, indicating the presence of bipolar disorder. Bipolar disorder should generally be treated with mood-stabilizing medications concurrent with the initiation of treatment for the substance use disorder.

In the treatment of mood disorders, the variety of treatment options has led to the development of and testing of treatment algorithms that outline potential sequences of treatments to be followed depending on the response to prior treatments (Crismon et al. 1999; Trivedi et al. 2004; Davis et al. 2007). The various treatment options for co-occurring substance and mood disorders (behavioral and medication treatments for substance use disorders, medication and behavioral treatments for mood disorders) suggest that similar algorithms might be developed and tested.

Acknowledgment Supported by grants P50 DA09236 (Dr. Kleber), U10 DA13035 (Dr. Nunes and Dr. Rotrosen), and K24 DA022412 (Dr. Nunes) and U10 DA15831 (Dr. Weiss and Dr. Carroll) and K24 DA022288 (Dr. Weiss).

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