

Current review of the comorbidity of affective, anxiety, and substance use disorders

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Purpose of review

This review will provide an update on the diagnoses treatment of co-occurring mood/anxiety and substance use disorders. Interest in co-occurring disorders is growing because of the prevalence and negative impact of comorbidity on course, treatment outcomes and prognoses of both disorders.

Recent findings

There have been a number of recent studies exploring psychotherapeutic and pharmacotherapeutic treatment of co-occurring disorders. In particular, serotonin reuptake inhibitors and/or buspirone have demonstrated efficacy in decreasing consumption and improving psychiatric symptoms in individuals with depression, social phobia and generalized anxiety disorder. There have been promising pilot studies exploring manual-guided psychotherapeutic interventions specifically targeting individuals with co-occurring substance use and post-traumatic stress disorder, depression and bipolar disorder.

Summary

The co-occurrence of substance abuse and mood and anxiety disorders is common and has important treatment implications. Recent investigations of pharmacotherapeutic and psychotherapeutic strategies specifically targeting individuals with comorbidity provide cause for optimism, but much work remains to be done.

Keywords

co-occurring disorders, mood disorders, anxiety disorders, dual diagnosis

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Abbreviations

ECA	Epidemiologic Catchment Area
GAD	generalized anxiety disorder
MAOI	monoamine oxidase inhibitor
NCS	National Comorbidity Study
OCD	obsessive-compulsive disorder
PTSD	post-traumatic stress disorder
SCID	Structured Clinical Interview for DSM-IV
SSRI	selective serotonin reuptake inhibitor
TCA	tricyclic antidepressant

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Introduction

There is a growing body of literature exploring the interface of mood and anxiety disorders and substance use disorders. It is clear that these disorders commonly co-occur and the relationship is complex and bidirectional. Two epidemiological surveys have emphasized the prevalence of comorbid mood/anxiety and substance use disorders in community samples: the National Institute of Mental Health Epidemiologic Catchment Area (ECA) study [1] and the National Comorbidity Study (NCS) [2]. In the ECA study, an estimated 45% of individuals with alcohol use disorders and 72% of individuals with a drug use disorder had at least one co-occurring psychiatric disorder. In the NCS, approximately 78% of alcohol-dependent men and 86% of alcohol-dependent women met lifetime criteria for another psychiatric disorder, including drug dependence. Interest in the co-occurrence of psychiatric and substance use disorders is clinically important because comorbidity has been found to have a negative impact on the course, treatment outcome, and prognosis of both syndromes. In this review, the relationship between substance use disorders and specific anxiety and mood disorders will be explored. The review will begin with an overview of some of the general principles of diagnosis and treatment of co-occurring disorders, then the relationship between individual mood and anxiety disorders and substance use disorders will be explored. Specifically, for each disorder the prevalence of co-occurrence with substance use, clinical characteristics and treatment of individuals with co-occurring disorders will be reviewed.

Diagnostic considerations

One of the more difficult tasks in assessing patients with co-occurring mood and anxiety symptoms and substance use disorders is the accurate diagnosis and differentiation between substance-induced states and primary psychiatric diagnoses. At times, the complex relationships between anxiety symptoms, affective symptoms, and substance-induced symptoms can lead to diagnostic uncertainty. Some individuals with anxiety or affective disorders may be self-medicating psychiatric symptoms with substances of abuse. Chronic and excessive use of some substances may unmask a genetic predisposition to psychiatric illness. It is also clear that intoxication and withdrawal from substances of abuse can mimic anxiety and affective illnesses.

While the best way to differentiate substance-induced transient symptoms from psychiatric illness is through observation during a period of abstinence, the duration of abstinence necessary for accurate diagnosis is controversial. The length of time abstinent should be based on both the diagnosis being assessed and the substance used. For example, long half-life drugs (e.g. some benzodiazepines, methadone) may require several weeks of abstinence for withdrawal symptoms to subside so that an accurate diagnosis may be made. For shorter-acting substances (e.g. alcohol, cocaine, short half-life benzodiazepines), however, both the acute intoxication and withdrawal duration are likely to be briefer and it may be possible to make valid diagnoses with shorter periods of abstinence. A family history of the particular psychiatric disorder, the onset of psychiatric symptoms before the onset of substance abuse and dependence, and sustained psychiatric symptoms during lengthy periods of abstinence all suggest a primary psychiatric illness.

Because of the high rate of co-occurrence of mood, anxiety and substance use disorders, screening patients presenting at either substance use or psychiatric treatment settings is critical. This is especially important considering that early diagnosis and treatment can improve treatment outcomes. There is increasing pressure from both psychiatric and substance use treatment settings to assess patients quickly and efficiently. Brief screening tools for substance use disorders that have been found useful in psychiatric settings include the Alcohol Use Identification Test [3], the Michigan Alcohol Screening Test [4] and the Drug Abuse Screening Test [5,6]. The Alcohol Use Identification Test is also useful in the identification of hazardous drinking in substance-dependent patients [7]. Screening for psychiatric disorders in substance abusers is an underinvestigated area and may be particularly problematic because of symptom overlap. The Symptom Checklist (SCL-90) and the Structured Clinical Interview for DSM-IV (SCID) are two widely used instruments for psychiatric screening and diagnoses. The SCL-90 [8] has been found to have moderate specificity and high sensitivity in screening for anxiety and mood disorders in substance use patients. One study found the concurrent discriminant and predictive validity of the SCID for anxiety disorder diagnoses in substance abusers to be poor [9]. This is probably because of the overlap of symptoms described above. Modified versions of the SCID such as the Psychiatric Research Interview for Substance and Mental Disorder have been designed to develop the chronological relationships between the psychiatric symptom and substance use for the purpose of diagnostic clarity [10]. Further work in this area will be important.

General treatment considerations

In general, treatment efforts addressing psychiatric and substance use disorders have developed in parallel. The integration of services and effective treatments from both fields will be critical to the optimal treatment of individuals with co-occurring disorders. It is particularly important to maximize the use of nonpharmacologic treatments. First, the ability to self-regulate subjective states and the confidence that can result from successful mastery through behavioral therapy can be extremely helpful to individuals in recovery. Second, learning strategies to self-regulate anxiety and mood symptoms may help patients to break out of the mindset of using external agents to combat intolerable subjective states and acquire alternative coping strategies. In terms of psychosocial treatments, cognitive behavioral therapies are among the most effective treatments for both anxiety and affective disorders [11]. Cognitive behavioral therapies also have demonstrated efficacy in the treatment of substance use disorders [12]. Behavioral therapies, such as relaxation, breathing and biofeedback techniques, are sometimes used in substance abuse treatment programs. These modalities can also be effective in the treatment of anxiety disorders and the management of anxiety symptoms. There has been promising pilot work investigating the integration of treatments into therapies specifically targeting co-occurring disorders, which will be discussed in the sections that follow.

Research investigating pharmacotherapies for both substance use and psychiatric disorders is progressing rapidly. Integration of information from both the psychiatric and substance abuse fields has led to the testing of strategies targeting individuals with both disorders. Specific co-occurring disorders are discussed in detail later, but general principles involved in choosing a pharmacological agent include paying particular attention to potential toxic interactions with drugs and alcohol should relapse occur, and assessing the abuse potential of the agent being used. Fortunately, there has been an influx of new psychopharmacologic agents with better safety and tolerability profiles in the past 10 years.

Anxiety disorders

In the following sections, specific anxiety disorders which commonly co-occur with substance use disorders will be reviewed. For each disorder, prevalence of comorbidity will be presented followed by a discussion of diagnostic issues and treatment options.

Panic disorder

Panic disorder is characterized by the occurrence of spontaneous panic attacks and at least 1 month of persistent worry of having another attack, concern about the implications of a panic attack, or avoidance of situations that might bring on a panic attack. This worry

and avoidance must produce functional impairment. Panic disorder can cause financial, social, and occupational impairment equal to that seen in depression.

The ECA study revealed a 1.5% lifetime prevalence of panic disorder among adults, with 36% having a co-occurring substance use disorder [1]. The risk of a comorbid substance use disorder in patients with panic disorder was 2.4 times higher than that in the general population [13]. Most of the literature examining panic disorder and substance use disorders has focused on alcoholism rather than substance abuse. The estimated prevalence of panic disorder and agoraphobia in alcoholic samples ranges from 5 to 42% [14]. This large diagnostic variability can be accounted for by the fact that panic symptoms are often seen during substance withdrawal syndromes and acute intoxication from a variety of substances of abuse. Therefore, differences in the timing of diagnosis can make large differences in prevalence estimates. Lower rates have been found in drug abusing populations as compared with alcoholic populations. In studies of methadone-maintained populations, 6.9–13% met criteria for panic disorder [15,16]. Cox and colleagues [17] studied 144 patients admitted for the treatment of a variety of substance use disorders and found that 33.8% of individuals with panic attacks reported using nonprescribed substances for reducing panic attacks. Cocaine-dependent individuals are less likely to endorse panic symptoms, with one large study estimating the prevalence of panic disorder to be 1.7% in a group of cocaine-dependent individuals [18].

While the idea of self-medication has been posited by some to explain the high comorbidity of panic and substance use disorders, many substances of abuse (cocaine/marijuana/other stimulants) may actually induce panic attacks or panic disorder during periods of acute intoxication [19,20] or withdrawal. Cocaine, amphetamine and phencyclidine act on the noradrenergic system, which may explain their ability to induce symptoms of panic. Several reports have noted that cocaine can precipitate panic attacks in individuals without previous panic disorder [20,21]. Panic attacks have also been noted to occur after the use of intranasal phencyclidine and in the context of both sedative-hypnotic and alcohol withdrawal [22]. Moran [19] described a series of six cases of patients presenting for treatment of panic disorder and agoraphobia who associated the onset of symptoms with marijuana use.

Many classes of medications have demonstrated efficacy in the treatment of panic disorder, including selective serotonin reuptake inhibitors (SSRIs), tricyclic antidepressants (TCAs), monoamine oxidase inhibitors (MAOIs) and benzodiazepines [23]. Caution should be

used when treating panic disorder with antidepressants such as TCAs and SSRIs as these agents may cause an initial activation leading to a worsening of panic symptoms. This worsening of symptoms may increase the risk of relapse to substance use. It is recommended to start with low-dose TCAs and SSRIs to avoid activation. The latency of onset of TCAs and SSRIs in the treatment of panic disorder is also of concern. Maximal effectiveness has been known to take as long as 2–6 weeks, which may also place a substance user at risk for relapse during the medication initiation period.

Extreme caution should be taken when prescribing MAOIs in substance-using populations. Dietary restrictions are necessary because MAOIs can interact with tyramine in the diet resulting in a hypertensive crisis. Moreover, MAOIs in combination with stimulant substances may precipitate a hypertensive crisis.

While clinical trials have demonstrated the efficacy of TCAs and the SSRIs in the treatment of panic disorder in nonsubstance-using patients [24], these agents have not been systematically examined in comorbid populations with panic disorder. Interestingly, the SSRIs have been shown by some investigators to have modest effects in decreasing alcohol consumption [25], particularly in subgroups of alcoholics [26]. While much work needs to be done in further defining the subgroup of alcohol-dependent individuals most likely to respond to SSRIs, these agents may be a logical choice for the patient with comorbid panic disorder and alcoholism.

Despite the effectiveness of benzodiazepines in the immediate relief of panic and other anxiety symptoms, the abuse potential of the agents limits their use in substance-using populations. As a rule, clinical lore states that benzodiazepines should be avoided in patients with a current substance use disorder and used with caution in those with a history of a substance use disorder. One review of the literature, however, calls into question the evidence supporting the idea that benzodiazepines should not be used in patients with a history of substance abuse or dependence [27]. Alternatively, in a recent study comparing the effects of carbamazepine (an anticonvulsant) to lorazepam (a benzodiazepine) in the treatment of alcohol withdrawal, it was found that both agents were equally effective in decreasing symptoms of withdrawal. In the post-treatment period, however, patients treated with carbamazepine drank significantly less than those treated with lorazepam [28]. This finding was felt to be related to a withdrawal syndrome from as little as 5 days of benzodiazepine treatment. Benzodiazepines may sometimes be considered as adjunctive medication in substance abusers with panic disorder during the early treatment phase when activation or

latency of onset of the antidepressants is an issue. In such cases, close monitoring for relapse and limited amounts of medication should be given.

In one small case series, patients with cocaine-induced panic disorder had substantial symptom improvement after treatment with carbamazepine or clonazepam [21]. Since repeated cocaine administration is associated with neuronal sensitization leading to increased limbic excitability [29], it has been hypothesized that this is the mechanism of cocaine-induced panic. Panic disorder in patients with comorbid psychostimulant use may be linked to a sensitization mechanism and may respond particularly well to anticonvulsant medications such as carbamazepine or valproate. This hypothesis warrants further investigation.

As with most anxiety disorders, panic disorder is quite responsive to nonpharmacologic treatment. Behavioral techniques, such as exposure and systematic desensitization, have been shown to be effective [11,30,31]. Relaxation therapy and supportive therapy may also be helpful in some cases [11].

Generalized anxiety disorder

Generalized anxiety disorder (GAD) is defined as excessive worry for 6 months or longer. The worry involves a number of different areas, is not based on fear of panic attacks or social interactions, is described as difficult to control and causes significant distress on a daily basis. The free-floating anxiety characteristic of GAD has substantial overlap with acute intoxication with stimulants and withdrawal from alcohol, sedative/hypnotics, and opiates. While many substance-abusing individuals report anxiety symptoms consistent with GAD, they may not meet diagnostic criteria for GAD because of difficulty determining the etiology of these symptoms. Chambless and colleagues [32] reported that among alcoholics, symptoms of GAD were indistinguishable from the effects of alcohol withdrawal. Withdrawal from other substances such as benzodiazepines, sedative/hypnotics, and opiates present similar problems for diagnosis.

The majority of studies estimate that GAD affects between 8.3 and 52.6% of alcohol-dependent individuals [14]. In one of the few studies examining GAD and drug abuse specifically, Massion *et al.* [33] studied 357 patients with panic disorder (with or without agoraphobia) or generalized anxiety disorder. Sixty-three, or 18%, of those examined had GAD only. Of those with only GAD, 11% had a history of substance abuse or dependence excluding alcohol abuse or dependence. The prevalence of GAD in methadone-maintained and cocaine-dependent individuals has been found to be 21% and 8%, respectively [34].

The treatment of GAD complicated by substance abuse is challenging. Multiple agents including SSRIs, TCAs, venlafaxine, and anticonvulsants have been found to be useful in reducing the symptoms of GAD in nonsubstance abusers. While benzodiazepines are effective in the treatment of GAD, their use in substance abusers, as noted above, is controversial. Buspirone is a nonbenzodiazepine anxiolytic with no abuse potential. In a 12-week, double-blind, placebo-controlled trial of 61 anxious alcoholics, the buspirone-treated group had greater retention in treatment and reduced anxiety, resulting in slower return to heavy alcohol consumption and fewer drinking days during the follow-up period [35]. Other studies of buspirone in alcoholic populations, however, have yielded mixed results [36]. In a placebo-controlled trial, McRae *et al.* [37] explored the use of buspirone in 28 methadone-maintained patients with high anxiety ratings and found decreased anxiety in the medication-treated group. While the data remain somewhat contradictory, it seems that buspirone remains a good choice in individuals with comorbid GAD and substance use disorders due to its lack of abuse potential.

As with panic disorder, nonpharmacologic treatments for GAD can be very useful. GAD can be effectively managed using relaxation, coping skills, and cognitive-behavioral therapy techniques [38,39]. Pharmacotherapy and psychotherapy are likely to complement one another in optimizing patient outcomes. Nonpharmacologic treatment strategies in conjunction with judicious pharmacotherapeutic management should be encouraged.

Social anxiety disorder

Social anxiety disorder is defined as a marked and persistent fear of situations in which an individual is exposed to unfamiliar people or to the scrutiny of others. Fear of being embarrassed or evaluated negatively is the hallmark of the disorder. This fear often leads to avoidance of feared situations and results in impairment in academic, occupational, and social functioning.

The lifetime prevalence of social anxiety disorder in the NCS [40] was found to be 13.3%, with a 7.9% 12-month prevalence. Individuals with social phobia have high rates of comorbidity with other psychiatric disorders, particularly with substance use disorders. Studies examining the relationship between alcohol abuse and dependence with social phobia have found rates of comorbidity ranging from 8 to 56% [14]. These increased rates may be due to alcohol's purported effect as a 'social lubricant'. Consistent with the self-medication hypothesis, individuals with social anxiety disorder reported that alcohol intake reduced social anxiety and that the onset of social phobia occurred prior to the onset of alcohol abuse/dependence [41]. While the occurrence of

social phobia in drug dependence has not been as well-studied, Myrick and Brady [42] found lifetime prevalence of social anxiety disorder in a cocaine-dependent population to be 13.9%. In nearly all cases, the social anxiety disorder preceded the onset of cocaine dependence. In addition, Milby and colleagues [15] found a 5.9% prevalence of social anxiety disorder in a methadone-maintained population.

Early recognition of the individual with comorbid social anxiety disorder and substance use is paramount to an improved chance of recovery because the social anxiety disorder may interfere with an individual's ability to engage effectively in treatment. The diagnosis is frequently overlooked unless specific symptomatology is thoroughly assessed. A lengthy period of abstinence may not be needed, as the fear of interaction in social situations, which is the core of social anxiety disorder, is not a specific feature of substance use or withdrawal. The social fears that occur only during periods of intoxication with marijuana or stimulants, however, should not be considered sufficient to meet diagnostic criteria for social anxiety disorder.

The treatment of the individual with comorbid social anxiety disorder and a substance use disorder should address both conditions. As most treatment facilities utilize group therapy or 12-step programs such as Narcotics Anonymous and Alcoholics Anonymous, individuals with social phobia may have considerable difficulty engaging and participating in such group-oriented activities [42]. In fact, these patients may be unfairly judged by the staff as not invested in treatment due to their avoidance of group activities. A treatment plan that includes individual therapy may prove to be more effective. Thevos and colleagues [43] compared cognitive-behavioral therapy to 12-step facilitation therapy in alcoholics with and without social anxiety disorder. Female, socially phobic alcoholics showed delayed relapse to drinking with cognitive-behavioral therapy but not with 12-step facilitation therapy. In addition, several types of nonpharmacological treatments such as systematic desensitization, imaginal flooding, graduated exposure, social skills training, and cognitive approaches have proven effective for patients with social anxiety disorder without comorbid substance abuse [44,45].

Few studies have specifically examined the efficacy of medication treatment of individuals with comorbid social anxiety disorder and substance abuse. However, many agents have been investigated in the treatment of social anxiety disorder [46]. Of these agents, the MAOIs, the reversible inhibitors of monoamine oxidase, the SSRIs, and the benzodiazepines have documented efficacy. Currently, only one medication, the SSRI paroxetine, has received US Food and Drug Administration approval

in the treatment of social anxiety disorder. In one placebo-controlled trial, gabapentin was also efficacious in the treatment of uncomplicated social anxiety disorder [47]. Several other agents such as venlafaxine, bupropion, ondansetron and buspirone may also have efficacy, but have not been well studied. In one small placebo-controlled trial of patients with social anxiety disorder and alcohol dependence, paroxetine improved alcohol outcomes and decreased symptoms of social anxiety [48]. In choosing a medication for the treatment of comorbid social anxiety disorder and substance abuse, the SSRIs, gabapentin or venlafaxine would be a reasonable first choice. As previously mentioned, SSRIs may have the additional benefit of producing modest decreases in alcohol consumption. Benzodiazepines, if used, should be monitored carefully and, as previously mentioned, may have a role in providing symptom relief to patients during initiation of SSRI treatment.

Obsessive-compulsive disorder

Obsessive-compulsive disorder (OCD) is characterized by obsessive thoughts and compulsive behaviors. Obsessions are recurrent and persistent thoughts, ideas, images or impulses that are experienced as intrusive and senseless. Compulsions are repetitive, purposeful, or intentional behaviors performed according to certain rules or in a stereotypical fashion. The compulsion is considered a coping strategy for the obsessional thinking. The ECA revealed a 1–2% lifetime prevalence of OCD in the general population [1]. Although OCD has been reported to coexist with many other psychiatric disorders [49], little has been reported about the comorbidity of OCD and substance use disorders.

In several studies of treatment-seeking alcoholics, 3–12% were reported to have OCD [14]. Based on data from the ECA study, the risk of developing OCD was estimated to be 5.6 times higher for individuals using both cocaine and marijuana as compared with individuals using no illicit substances [50]. The odds ratio for OCD among those with marijuana use alone was 2.1, and 3.2 for cocaine, marijuana and at least one other substance. Milby and colleagues [15] found that 2.9% of the methadone-maintained individuals they studied met criteria for OCD.

Diagnosing OCD in substance abusers is somewhat less problematic than other anxiety disorders because substance use and withdrawal and OCD have fewer overlapping features and the characteristic symptoms of OCD are distinctive. A few case reports have noted some similarities to OCD in substance abusers: compulsive foraging for misplaced cocaine has been noted in cocaine addicts [51] and transient, obsessive-compulsive symptoms in individuals during intoxication with opiates [52] and hallucinogens [53]. The mechanism by which

substances of abuse may produce these symptoms remains unclear.

While several serotonergic medications have received US Food and Drug Administration approval for the treatment of OCD, there are no controlled trials or case reports of the treatment of comorbid OCD and substance abuse. Clomipramine and SSRIs are both efficacious in the treatment of OCD [23]. There are several areas of concern with the use of clomipramine in substance-abusing patients, however. Clomipramine, like other TCAs, may lower the seizure threshold. This is of particular concern in withdrawal states associated with alcohol and benzodiazepines. Toxic interactions with alcohol, stimulants and central nervous system depressants are also more likely to occur with clomipramine. For these reasons, SSRIs are recommended as the first line of treatment in individuals with OCD and a substance use disorder since there are fewer side effects or potential toxic interactions.

The combination of psychotherapy with pharmacotherapy is particularly important in the treatment of OCD [54]. Cognitive-behavioral therapies including thought-stopping, exposure, and response prevention have convincingly and reliably been shown to be extremely effective in the treatment of OCD [55,56]. Again, a synergistic effect of the pharmacotherapy and psychotherapy might be expected.

Post-traumatic stress disorder

Post-traumatic stress disorder (PTSD) is one of the most common anxiety disorders in individuals with substance use disorders. In the NCS, the odds ratio for substance use disorders was 2–3 for men and 2.5–4.5 for women with PTSD [57]. Using data from the ECA study, Cottler and colleagues [58] compared assault histories and PTSD in individuals with a substance use disorder with those without a substance use disorder. Of all subgroups studied, cocaine/opiate users were most likely to report a PTSD-qualifying traumatic event (43%), and the overall rate of PTSD was 10 times higher among these individuals compared with individuals without a substance use disorder. Reports from treatment-seeking samples of substance abusers also indicate a high prevalence of PTSD. In a number of studies of either drug or alcohol use disorders, lifetime prevalence of PTSD was found to be between 36 and 50%, and the current prevalence of PTSD between 25 and 42% [59–61].

It is likely that substance use (in particular, cocaine use) and repeated withdrawal (in particular alcohol, sedative hypnotic and opiate withdrawal) will exacerbate symptoms of PTSD. Cocaine use is associated with paranoia, hypervigilance, sleep disturbance, and autonomic arousal, all of which are features of PTSD. Alcohol, sedative-

hypnotic and opiate withdrawal are marked by feelings of anxiety and autonomic nervous system hyperactivity, which are believed to have as their origins excessive firing of neurons in the locus ceruleus [62]. It is possible that common pathophysiologic mechanisms are responsible for the symptom overlap and exacerbation of symptoms in individuals with comorbid PTSD and substance dependence.

Little is known about the effective treatment of patients with comorbid PTSD and substance abuse/dependence. While the treatment of PTSD is generally multimodal, pharmacotherapy is playing an increasingly important role. One important goal of pharmacotherapy is to reduce key symptoms of PTSD such that individuals can put greater distance between themselves and the traumatic event(s) without the use of alcohol or nonprescribed substances.

TCAs and MAOIs were shown in double-blind, placebo-controlled trials to improve intrusive and depressive symptoms of PTSD [63]. There are also uncontrolled reports of the positive effects of carbamazepine, beta blockers, clonidine, benzodiazepines, and lithium. More recently, a number of placebo-controlled trials with relatively large numbers of patients have demonstrated that SSRIs, specifically sertraline, fluoxetine and paroxetine, are useful in the treatment of PTSD [64–67]. A pilot study of sertraline treatment of PTSD in individuals with co-morbid alcohol dependence demonstrated a positive effect of sertraline in improving symptoms of PTSD and decreasing alcohol consumption [68].

The psychotherapeutic treatment of comorbid PTSD and substance abuse has been an area that has received much recent attention. Previously, the conventional approach was to treat the substance use and defer treatment of PTSD. This approach can be problematic because the symptoms of PTSD (e.g. sleep disturbance, intrusive thoughts) may drive relapse to substance use. Several studies investigating manual guided psychotherapeutic strategies specifically targeting co-occurring PTSD and substance dependence have shown preliminary success [69,70]. Further investigation of this important area is clearly warranted.

Affective disorder

In the following sections, specific anxiety disorders which commonly co-occur with substance use disorders will be reviewed. For each disorder, prevalence of comorbidity will be presented followed by a discussion of diagnostic issues and treatment options.

Depression

Symptoms of mood instability and depression are among the most common psychiatric symptoms seen in

individuals with substance use disorders. In the ECA study, 32% of individuals with an affective disorder also had a comorbid substance use disorder [1]. Of the individuals with major depression, 16.5% had an alcohol use disorder and 18% had a drug use disorder; and 56.1% of individuals with bipolar disorder had a substance use disorder. In both the ECA study and the NCS, bipolar disorder was the Axis I condition most likely to occur with a substance use disorder.

Studies in treatment-seeking samples have resulted in variable estimates of the comorbidity of affective illness with substance use disorders. One reason for this is that diagnostic issues at the interface of affective illness and substance use disorders are particularly complex. Estimates of the prevalence of depressive disorders in treatment-seeking, alcoholic individuals range from 15 to 67% [71]. In studies of cocaine-dependent individuals, estimates of affective comorbidity range from 33 to 53% [72]. Bipolar disorders appear to be more prevalent (20–30%) among cocaine-dependent individuals than among alcoholic individuals. In opiate-dependent samples, rates of lifetime affective disorder (primarily depressive disorders) range from 16 to 75% [73].

Studies of TCA treatment of major depressive episodes and alcoholism indicate that such treatment modestly decreases alcohol use and the symptoms of depression [74,75]. Serotonin has been implicated in the control of alcohol intake. A number of SSRIs have been shown to modestly decrease alcohol consumption in persons with problem drinking as well as in alcoholic individuals [76]. In a recent study investigating the use of fluoxetine in a group of alcoholic persons with major depression [77], individuals who received fluoxetine had significantly greater reduction in both depressive symptoms and alcohol consumption compared with the placebo group. This study is particularly important because the clinical improvement was more substantial than that seen in the studies involving TCAs, and SSRIs have less potential for toxicity and interaction with drugs of abuse than do TCAs.

Several trials of TCAs have been performed with opioid-dependent patients. Nunes and colleagues [78] found that imipramine significantly decreased depression in a group of depressed patients receiving methadone maintenance. The effect of imipramine on drug use was less marked. Although self-report measures indicated significantly less craving and drug use, there were no differences in positive urine drug screens.

The primary focus of use of TCAs in cocaine-dependent patients has been on treatment of cocaine dependence, rather than on treatment of depression. Several studies involving desipramine have shown improvement in anhedonia and cocaine craving and increased initial

abstinence in nondepressed patients, and one small study showed improvement in depressed patients [79]. Clinicians should be aware, however, that desipramine may have an activating effect in cocaine-dependent individuals, which can precipitate relapse, and, should relapse occur, desipramine may have additive cardiotoxicity in combination with cocaine. Unlike the promising data investigating the use of SSRIs in comorbid alcohol dependence and major depression, recent placebo-controlled trials investigating the use of fluoxetine in depressed cocaine-dependent [80••] and methadone-maintained [81] individuals have shown no effect of medication on drug use or symptoms of depression.

In conclusion, for the pharmacotherapeutic treatment of comorbid alcohol dependence and major depression, data support the use of SSRI agents. For cocaine- and opiate-dependent individuals with major depressive episode, there are limited data supporting the use of TCAs, but studies thus far testing the efficacy of SSRIs have been negative. It is possible that the different pharmacologic properties of these substances of abuse are involved in determining pharmacologic specificity in treatment responsiveness. Trials of some of the newer antidepressants with mixed 5HT/NE activity (venlafaxine/duloxetine) in alcohol-, cocaine- and opiate-dependent individuals with major depressive episode would be of interest in this regard.

Bipolar disorder

There are few published data on the treatment of bipolar disorder complicated by substance abuse. Lithium has been the standard treatment for bipolar disorder for several decades; however, substance abuse may be a predictor of poor response to lithium [82]. Patients with mixed manic episodes or rapid-cycling disorder have a better response to anticonvulsant drugs compared with lithium. Patients with bipolar disorder and concomitant substance use disorders appear to have more mixed or rapid-cycling episodes and therefore may have a better treatment response with anticonvulsant mood-stabilizing medications. Controlled studies testing this hypothesis need to be done. Weiss and colleagues [83] reported better medication compliance with valproate, compared with lithium, in a group of substance-abusing patients with bipolar disorder. Brady and colleagues [84] recently reported on results from a placebo-controlled, double-blind trial in which carbamazepine showed preferential efficacy in decreasing cocaine use in cocaine-dependent individuals with affective disorder as compared with those without affective disorders.

Psychotherapeutic treatment

The psychotherapeutic/psychosocial strategies used in the treatment of comorbid conditions should be speci-

fically tailored and contain elements of effective treatment from the areas of both substance abuse and affective disorders. Many of the principles of cognitive-behavioral therapy are common to the treatment of affective disorder as well as substance use disorders. There are several recently published pilot studies demonstrating efficacy for psychotherapeutic strategies specifically designed for dually diagnosed populations. Brown and colleagues [85] demonstrated that alcoholics with depressive symptoms had improved outcomes at 3- and 6-month follow-up visits after treatment with cognitive-behavioral treatment for depression as compared with a relaxation training control. Weiss and colleagues [86] compared a manual-based group therapy for patients with bipolar disorder and substance dependence with treatment as usual and found that patients receiving the group treatment had significantly better outcomes in a number of domains. Alcoholics Anonymous and Narcotics Anonymous are found in all communities, and active participation can be a major factor in an individual's recovery. It is important that dually diagnosed individuals choose 12-step recovery groups in which they are not likely to receive mixed or negative messages about the use of psychotropic medications under the directions of a physician. Further work is needed in developing therapies specifically geared toward individuals with comorbid affective and substance use disorders in which therapeutic techniques for each type of disorder are combined.

Conclusion

The interest in the co-occurrence of mood and anxiety disorders and substance use disorders has grown tremendously in the past 10 years. It is clear that co-occurrence of these disorders is common and has an impact on prognosis and treatment. The diagnostic issues at the interface of substance or alcohol use disorders and affective and anxiety disorders are particularly difficult because of the substantial symptom overlap between substance intoxication and withdrawal, and symptoms of mood and anxiety disorders.

Advances have been made in the treatment of co-occurring disorders. In terms of psychotherapeutic treatments, several manuals specifically targeting treatment of patients with PTSD, depression and bipolar disorder and substance use disorders have been developed. Further investigation of specifically tailored treatments for patients with co-occurring substance use and other mood and anxiety disorders is underway. Many advances have been made in pharmacotherapy of mood and anxiety disorders in the past 10 years. This progress impacts the population with co-occurring disorders because the newer agents have less toxicity, fewer side effects and interactions with substances of abuse. While there are not many studies specifically

targeting pharmacotherapy for co-occurring disorders, those that have been conducted indicate that similar pharmacotherapeutic agents work for mood and anxiety disorders with or without substance use disorders. Furthermore, treatment of mood and anxiety disorders may be associated with decreased substance use. Clearly, specific considerations in choosing a pharmacologic agent for use in patients with substance use disorders include safety, toxicity and abuse liability. In conclusion, although the co-occurrence of substance abuse and mood and anxiety disorders is an important area in which recent developments provide cause for considerable optimism, much work remains to be done.

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Papers of particular interest, published within the annual period of review, have been highlighted as:

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- of outstanding interest

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