CHAPTER 15

Co-Occurring Substance Use Disorders and Other Psychiatric Disorders

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Determining better ways to identify and treat individuals with co-occurring substance use disorders (SUDs) and other psychiatric disorders has become increasingly important from clinical, research, and policy perspectives. Several observations have driven this imperative: (1) Co-occurring SUDs with other psychiatric disorders are prevalent (Conway, Compton, Stinson, & Grant, 2006; Kessler et al., 1996; Regier et al., 1990; Swendsen et al., 2010) and associated with worse clinical and functional outcomes than either SUDs or other psychiatric disorders alone (Hser et al., 2006; Mueller et al., 1994; Ritsher et al., 2002); (2) many people with these co-occurring disorders do not receive adequate treatment (Substance Abuse and Mental Health Services Administration [SAMHSA], 2002); and (3) compared to psychiatric patients without co-occurring SUDs, patients with co-occurring disorders tend to use more costly treatments such as emergency and hospital care (Dickey & Azeni, 1996; Mark, 2003). Together, these observations have led to the development of specific new treatments designed or adapted for this population.

Within SUD populations, multiple SUDs are common (Conway et al., 2006; Kessler et al., 1997; Regier et al., 1990; Swendsen et al., 2010). While these individuals also may be considered "dually diagnosed," this chapter focuses exclusively on patients who have an SUD plus a non-SUD co-occurring psychiatric disorder. We refer to non-SUD psychiatric disorders simply as "psychiatric disorders" to distinguish them from SUDs. Additionally, this chapter excludes co-occurring nicotine dependence and psychiatric disorders, a topic that is important and broad enough to require independent attention (Ziedonis et al., 2008; see Chapter 6, this volume).

In this chapter, we review psychosocial and psychopharmacological treatments for patients with co-occurring SUDs and other psychiatric disorders.

EPIDEMIOLOGY

Studies in SUD and psychiatric treatment-seeking populations (McLellan & Druley, 1977; Ross et al., 1988) have suggested high prevalence rates of co-occurring SUDs and psychiatric disorders. However, treatment-seeking samples may not be representative of community populations, since they tend to have higher rates of comorbidity and may have more severe manifestations of the disorder for which they are seeking treatment. Thus, epidemiological studies of prevalence rates in community populations are important in assessing the true comorbidity prevalence rate.

The National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) is the largest and most recent study to date that examines the epidemiology of SUDs and co-occurring psychiatric disorders in a community sample. Conducted in 2001–2002, with a follow-up reinterview wave carried out in 2004–2005, NESARC specifically sought out data on co-occurring conditions, asking questions about alcohol, tobacco, and other substance use, along with inquiries on psychiatric/psychological disorders, family history and medical conditions, and gambling, among others. Data were collected from randomly selected individuals based on household data from the 2000 Census, with an 81% response rate. NESARC results demonstrate that SUDs and psychiatric disorders are commonly co-occurring in community populations (Compton et al., 2007; Hasin et al., 2007; Hasin & Kilcoyne, 2012). When adjusted for other sociodemographic factors, lifetime alcohol use disorder was significantly associated with mood disorders (odds ratio [OR] = 2.4), anxiety disorders (OR = 2.3), and personality disorders (OR = 2.8). Likewise, 12-month and lifetime drug use disorders were significantly associated with alcohol use disorders, nicotine dependence, and mood, anxiety, and personality disorders (ORs = 2.2–9.0).

The two previous major psychiatric epidemiological studies, the Epidemiologic Catchment Area (ECA) study (Regier et al., 1990) and the National Comorbidity Study (NCS), carried out from 1990 to 1992 (Kessler et al., 1996), similarly demonstrate that co-occurring SUDs and psychiatric disorders are prevalent in community populations. Methodological advancements of the NCS included an expanded scope of the community sample (e.g., the ECA sampled from within five U.S. communities; the NCS sampled nationally representative households) and an advanced version of the *Diagnostic and Statistical Manual of Mental Disorders* (i.e., DSM-III-R; American Psychiatric Association, 1987). Also, while both studies surveyed most of the more common psychiatric disorders, the ECA did not include posttraumatic stress disorder (PTSD), whereas the NCS did. Neither epidemiological survey included Axis II disorders other than antisocial personality disorder. Despite these limitations and differences between the two studies, their results were often qualitatively similar, although the magnitude of their estimates differed somewhat at times. Among persons with psychiatric disorders, the ECA estimated that 30% had a co-occurring SUD. The prevalence varied by diagnosis, however; co-occurring SUDs were most common in individuals with antisocial personality disorder, followed by those with

bipolar I disorder. In SUD populations, the ECA and NCS estimated that over half would experience psychiatric disorders in their lifetime. These lifetime estimates do not merely reflect rare or historical periods in an individual's history; the 12-month comorbidity prevalence rate of these disorders was also quite high. For example, the NCS estimated that over 33% of those with bipolar disorder experienced an SUD within 12 months, followed by nearly 20% of those with major depression and 15% of those with an anxiety disorder. From 2001 to 2003, a substantial portion (87.6%) of the NCS study population was reinterviewed in the National Comorbidity Survey–2 (NCS-2; Swendsen et al., 2010), allowing for updated diagnostic assessments (i.e., based on DSM-IV-TR; American Psychiatric Association, 2000) and demonstrating significant prospective risks posed by baseline mental disorders for the onset of SUDs in the follow-up time frame.

In Australia, the 2007 National Survey of Mental Health and Wellbeing (NSMHWB) revealed similarly high rates of comorbidity compared to the U.S. surveys, with 25.4% of individuals with an anxiety, affective, or SUDs having at least one other class of disorder (Teesson, Slade, & Mills, 2009). In particular, the NSMHWB estimated that individuals with an alcohol use disorder were more than twice as likely to have an anxiety disorder and were 4.5 times more likely to have any mental disorder compared to the rest of the sample (Teesson et al., 2010).

THE RELATIONSHIP BETWEEN SUBSTANCE ABUSE AND PSYCHOPATHOLOGY

While determining which disorder is primary in patients with co-occurring SUDs and psychiatric disorders can be useful in clinical research, it may provide little benefit in the clinical management of these patients. Patients with two disorders typically require treatment for both. In patients with co-occurring cannabis dependence and psychosis, for example, it is interesting scientifically to consider whether cannabis use led to the development or earlier onset of psychotic illness or vice versa (Moore et al., 2007), but clinically, patients require both SUD and psychiatric treatment to be helped most effectively. On the other hand, the exception is patients who present with temporary psychiatric symptoms caused by the substance use or its withdrawal, which resolve with treatment; an example of this would be psychosis induced by methamphetamine use (Grelotti, Kanayama, & Pope, 2010).

Meyer (1986) offered a now-classic framework to consider six possible ways in which SUD and other psychopathology may be related:

1. *Psychopathology may be a risk factor for SUDs.* As described previously, studies of patient and community samples indicate that the risk of having a co-occurring SUD is elevated in persons with psychiatric disorders. For example, dopaminergic dysfunction in patients with schizophrenia has been hypothesized to increase their risk of SUDs—particularly cocaine use disorders (Green et al., 1999; Smelson et al., 2002b). Another theory, widely known as the "self-medication hypothesis" (Khantzian, 1989, 1997; Khantzian & Albanese, 2008), suggests that psychopathology leads patients to use substances in an attempt to decrease unwanted psychiatric symptoms.

For example, a patient with insomnia due to PTSD nightmares may use alcohol or marijuana to induce sleep. Although research has not found direct connections between particular psychopathological symptoms and specific substances (rather, patients tend to misuse a wide variety of substances to "treat" a range of symptoms), the general principle is an important one. It is discussed in more detail in the next item.

2. *Psychiatric disorders and co-occurring SUDs may serve to modify the course of each other in terms of symptomatology, rapidity of onset, and response to treatment.* Also, as we described more below, there is considerable evidence that comorbidity is associated with worse outcomes. For example, there is evidence that patients with schizophrenia and co-occurring SUDs do not respond as well to similar doses of first-generation antipsychotic medications as those without SUDs (Bowers et al., 1990).

3. *Psychiatric symptoms may result from chronic intoxication.* Drug and alcohol use can result in a variety of psychiatric symptoms, such as depression, anxiety, euphoria, psychosis, and dissociative states. Most such symptoms disappear, however, within hours (e.g., cocaine-induced paranoia; Satel et al., 1991) to weeks (e.g., alcohol-induced anxiety or depression; Brown et al., 1991; Brown & Schuckit, 1988).

4. *Long-term substance use can lead to psychiatric disorders that may not remit.* Alcohol-induced, long-term cognitive changes, such as those seen in alcohol-induced persisting dementia, exemplify one way in which chronic use of a substance can create enduring change.

5. *Substance abuse and psychopathological symptoms may be meaningfully linked.* Some individuals may use alcohol or drugs in ways that enhance their psychiatric symptoms. For example, patients with antisocial personality disorder who seek disinhibition and aggression may use alcohol or cocaine, and patients with bipolar disorder may use cocaine or other stimulants to augment a euphoric mood (Weiss et al., 1986, 1988).

6. *The SUD and psychiatric disorder may be unrelated.* The presence of two disorders within an individual does not imply a causal link. For example, both alcohol dependence and depressive disorders are common in the general population; many people with both disorders are not depressed because they drink, nor do they drink because they are depressed. As another example, Brunette et al. (1997) studied the relationship between severity of substance abuse and severity of schizophrenic symptoms in patients diagnosed with both disorders, and found weak relationships and no consistent patterns of relationships between the two sets of symptoms.

The "Self-Medication Hypothesis"

One potential explanation for the increased prevalence rate of co-occurring SUDs among patients with psychiatric disorders has been the "self-medication hypothesis" (Khantzian, 1985, 1997; Khantzian & Albanese, 2008), which postulates that certain drugs may be particularly reinforcing for particular patients because of their specific psychopathology.

Two fundamental assumptions underlie this hypothesis: first, that substances are abused to relieve psychological pain, not just to create euphoria; and second, that there is specificity between patients' "drug of choice" and the particular intolerable emotions or symptoms that they are attempting to alleviate. For example, patients with social anxiety may be drawn to alcohol to decrease their symptoms, while patients who are prone to violence and anger outbursts may prefer the calming effects of opioids to the potentially disinhibiting effects of alcohol. Another recently discussed example might be the high prevalence of nicotine use in patients with schizophrenia, who might be drawn to smoking cigarettes (due to biological predispositions based on alterations in nicotinic acetylcholine receptors) as a way to modulate antipsychotic medication side effects or to self-medicate negative symptoms and cognitive deficits (Dalack et al., 1998; Winterer, 2010).

A major criticism of the self-medication hypothesis has been its heavy reliance on anecdotal data from patients in psychotherapy and the relative paucity of empirical studies testing it (Aharonovich et al., 2001). Additionally, intoxicants may produce very different effects acutely compared to the effects of chronic administration. Studies of individuals with heroin (Meyer & Mirin, 1979), cocaine (Post et al., 1974), and alcohol (Mendelson & Mello, 1966) use disorders have indicated a dichotomy between the acute effects of these drugs in producing euphoria or tension relief and the chronic or high-dose effects in producing dysphoria. Several researchers have sought to test empirically the self-medication hypothesis in larger samples. The results have tended not to support the specificity of using a particular addictive substance to alleviate specific psychopathology or mood states (Aharonovich et al., 2001; Weiss, Griffin, et al., 1992). However, while not necessarily a validation of the theory that patients use addictive substances to alleviate certain mood states, there is evidence that treating a co-occurring psychiatric disorder (Cornelius et al., 1997; Greenfield et al., 1998) and remission of its symptoms (Hasin et al., 1996) can improve SUD outcomes.

Other Theories

Weiss (1992) suggests three additional mechanisms by which psychopathology can make an individual more vulnerable to SUDs.

1. *Psychopathology may interfere with an individual's judgment or ability to appreciate consequences.* Individuals with psychiatric disorders may be more vulnerable to SUDs, because the impaired judgment that is often present in many psychiatric syndromes can interfere with one's ability or willingness to understand or change one's behavior. For example, severely depressed patients may have insight regarding the destructive effect of their drinking but continue to drink due to the pessimism about the possibility and value of change that is part of their depressive disorder. Similarly, the recklessness, irritability, and grandiosity of patients with mania or hypomania may interfere with their capacity to appreciate the harmful nature of their substance use.

2. *Psychopathology may accelerate the process of substance dependence by leading to more dysphoria either during chronic use or early abstinence.* It is possible

that patients with underlying psychopathology may experience more dysphoria from chronic substance use or more severe withdrawal symptoms when discontinuing drugs or alcohol. Although this potential mechanism has received little study, there is some evidence that cocaine abusers with major depressive disorder may report more severe mood symptoms during abstinence compared to cocaine abusers without depression (Gawin & Kleber, 1986).

3. *Psychopathology may reinforce the social context of drug use.* Some patients with severe psychiatric illness may be drawn to a drug-using subculture because they feel it facilitates socialization or a new peer group. For example, some patients with schizophrenia have described using substances to socialize or be accepted by peers, even though substances increased the risk of psychosis (Drake et al., 1989; Spencer et al., 2002).

Thus, multiple possible motivations and causes contribute to the initiation and maintenance of problematic alcohol and drug use in patients with psychiatric disorders.

DIAGNOSING PSYCHIATRIC DISORDERS IN PATIENTS WITH SUDs

The task of determining whether a patient is suffering from a substance-induced disorder or an independent psychiatric disorder can be complicated and has not been well-studied (Morojele et al., 2012; Torrens et al., 2011). Substances of abuse can cause a wide range of psychiatric symptoms. Clinicians evaluating such patients need to determine whether the disturbance is independent of substance use or related to intoxication or withdrawal. For example, when examining a patient who has a long history of alcohol dependence and depressive symptoms, it can be difficult to determine whether the depressive symptoms result from the direct pharmacological effects of alcohol, the many losses experienced as a result of the alcohol use, feelings of discouragement about the inability to stop drinking, or an independent mood disorder. Other etiologies, such as metabolic disturbances, head trauma, and personality disorders, must also be considered in the differential diagnosis of depressive symptoms in alcohol-dependent patients (Jaffe & Ciraulo, 1986). In a recent study, Torrens et al. (2011) compared risk factors for substance-induced versus independent psychiatric disorders in a population with co-occurring SUDs and psychiatric disorders. They found that mood and anxiety disorders were more likely to be independent. Subjects recruited from nontreatment setting were more likely to have substance-induced disorders than were subjects recruited from a treatment setting (OR = 3.5).

Given these considerations, one could ideally establish diagnostic rules to assist in determining whether a psychiatric syndrome is due to substance use or represents a separate and independent disorder. For example, some clinicians may establish a rule that a patient must be abstinent from alcohol and drugs for at least 4 weeks before one can make a diagnosis. Unfortunately, one does not always have the luxury of observing such lengthy abstinent periods (either by historical report or in the present) in which to assess this. In such circumstances, guidelines, as opposed to strict

rules, can be helpful. For example, several studies have observed that for alcohol-dependent patients with major depressive disorder, treating the depression can have a positive impact on drinking (Cornelius et al., 1997; Greenfield et al., 1998). Thus, while DSM-5 (American Psychiatric Association, 2013) criteria for substance-induced depressive disorder suggest at least 4 weeks of symptom persistence during abstinence before a clinician can diagnose an independent depressive disorder, it also notes that clinicians can diagnose an independent disorder if other convincing factors are in place (e.g., a history of recurrent non-substance/medication-related episodes or symptoms that preexisted before onset of substance use). Certain disorders, such as eating disorders and PTSD, can be diagnosed readily, even in the context of substance use or withdrawal, since their symptoms do not closely resemble substance-related syndromes. Indeed, for a diagnosis such as PTSD, which tends to be underdiagnosed in patients with SUDs, the greater danger is to delay diagnosis; waiting for a period of abstinence may prevent needed treatment for the co-occurring disorder (Najavits, 2004).

Finally, clinicians should consider whether the patient's symptoms are what would be expected upon discontinuation of the abused substance. If there is considerable overlap between the observed symptoms and what one would expect from the drug discontinuation syndrome, then the clinician should wait until (1) the symptoms resolve, or (2) no longer are consistent with what would be expected with drug cessation (i.e., the syndrome one would expect to see after 1 week versus 1 month of alcohol abstinence). Alternatively, if there is little overlap between the symptoms observed and the expected abstinence syndrome (e.g., bulimia nervosa in an opioid-dependent patient), then the diagnosis can be made without waiting for an extended abstinent period.

DIAGNOSING SUDs IN PATIENTS SEEKING TREATMENT FOR PSYCHIATRIC DISORDERS

Co-occurring SUDs are often overlooked in patients seeking treatment for psychiatric disorders. The first step in the accurate diagnosis of SUDs is systematically to ask the patient about the presence of substance use. Structured clinical assessments have been demonstrated to improve detection of SUDs compared to routine assessment in outpatient severe and persistently mentally ill (SPMI; Breakey et al., 1998) and inpatient (Albanese et al., 1994) populations; they have also outperformed urine toxicology testing (Albanese et al., 1994). Unfortunately, the increasing acuity of patients on inpatient units and the demanding time constraints of outpatient psychiatric practice (Woodward et al., 1991) may pose challenges to the systematic assessment of SUDs. In one outpatient study, combining multiple standardized clinical instruments improved rates of detection but raised similar concerns about time constraints of routine clinical work and resultant underdetection (Wusthoff et al., 2011). In another outpatient study, adding the four-item CAGE (Cut down, Annoyed, Guilty, Eye-opener) Questionnaire (Ewing, 1984) improved the sensitivity of detecting SUDs from 62 to 97% in an SPMI population (Breakey et al., 1998). However,

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self-report alone, without urine toxicology, can also lead to underdetection of substance use (Claassen et al., 1997).

Finally, contingencies play an important role in patients' willingness to self-report substance use. If patients are repeatedly encouraged to be honest in their self-reports, and if they are told (and more importantly, if they believe) that there will be no negative consequences of reporting use (e.g., being discharged from a treatment program or reported to a probation officer or employer), then they are more likely to be forthcoming in reporting their use. If, however, they are concerned that there will be negative consequences, then they are less likely to do so. Thus, self-reports of use in an emergency department, where a patient is unlikely to know the clinician and will probably not believe (whether it is true or not) that there will be no negative consequences for disclosing use, are likely to be suspect. However, in an outpatient treatment setting, in which a patient has an opportunity to build a relationship with a clinician or treatment team, and perhaps sees other patients self-disclosing and benefiting from that disclosure, self-reports are likely to be more valid (Weiss et al., 1998).

TREATMENT OF PATIENTS WITH CO-OCCURRING SUDs AND OTHER PSYCHIATRIC DISORDERS

Association between Co-Occurring Disorders and Treatment Outcome

In both SUD and psychiatric treatment-seeking populations, patients with co-occurring SUDs and psychiatric disorders typically experience worse outcomes than their "singly diagnosed" peers (Ritsher et al., 2002; Schaar & Oejehagen, 2001; Najavits et al., 2007). However, there are specific populations in which the evidence is mixed, such as populations with SPMI (Farris et al., 2003; Gonzalez & Rosenheck, 2002) and antisocial personality disorder (Cacciola et al., 1995; Kranzler et al., 1996). The effect of other psychiatric disorders on SUD outcomes may vary by SUD type. For example, whereas co-occurring major depression appears to predict worse alcohol outcomes (Brown et al., 1998; Greenfield et al., 1998), there is less evidence for its predicting worse cocaine outcomes (McKay et al., 2002; Rohsenow et al., 2002).

There is also evidence (albeit somewhat inconsistent) that gender may play a role in mediating the effect of co-occurring psychiatric disorders on SUD outcome. Major depression in men has been associated with worse SUD outcome (Compton et al., 2003; Rounsaville et al., 1987), although this is not a consistent finding (Kranzler et al., 1996; Powell et al., 1992). In contrast, some studies suggest that female gender has been associated with similar or better SUD outcomes among patients with co-occurring psychiatric disorders (Compton et al., 2003; Rounsaville et al., 1987), except for phobia, which was associated in one study with worse SUD outcome in women (Compton et al., 2003). Finally, whereas antisocial personality disorder in men has been associated with worse outcomes (Compton et al., 2003; Kranzler et al., 1996), the evidence in women has been mixed (Compton et al., 2003; Rounsaville et al., 1987).

A Heterogeneous Population

Since patients with co-occurring disorders comprise a heterogeneous population, it follows that their treatment should perhaps reflect that heterogeneity (Weiss, Mirin, et al., 1992); a "one size fits all" approach therefore will likely not be optimal. However, providing group treatments tailored to patients with some degree of diagnostic homogeneity (e.g., patients with bipolar disorder and SUDs) can be a difficult strategy to implement if one is unable to recruit a large enough clinical population for these groups. Similarly, even within diagnostically homogeneous groups, considerable heterogeneity in illness severity and functioning may still exist. Ries et al. (1997) have suggested a conceptual approach that divides patients with co-occurring SUDs and psychiatric disorders into four major subgroups, according to the severity (i.e., major or minor) of each disorder. Although this is a somewhat crude way to classify patients, it may be helpful in developing an outpatient group treatment program for patients with co-occurring disorders.

An additional consideration is that not all patients are similar in terms of insight regarding their SUD, nor are they similarly ready to address it. Thus, patients who cannot decide whether to address their substance use may do better in a group focused on resolving that issue, as opposed to a group in which all participants are actively engaged in treatment and making lifestyle changes to support sobriety. We know of no studies, however, that have tested this idea empirically. It is possible, for example, that having a mix of patient severity levels in one group gives patients the opportunity to learn from those further along in their recovery. This is a central principle of Alcoholics Anonymous, and it appears to have strong anecdotal support. Treatments that focus on particular co-occurring diagnoses (e.g., bipolar patients with SUDs) also have not been directly compared to more general thematic groups (e.g., co-occurring disorder groups that are more general, encompassing a wide variety of diagnoses). Thus, it remains an empirical question how the heterogeneity of patients with co-occurring SUDs and psychiatric disorders should best be addressed within the realistic constraints of specific clinical settings.

Sequential, Parallel, and Integrated Treatment Models

There are three major models in which patients with co-occurring SUDs and psychiatric disorders are treated: sequential, parallel, and integrated treatment. We discuss each below.

In *sequential treatment*, the more acute condition is treated first, followed by the less acute co-occurring disorder. Often, this sequential approach is attempted when one condition is perceived to be more acute than another. Sometimes, however, it may occur because of the perception that one condition is secondary to another, that staff may not be trained to treat it, or because the condition is perceived as iatrogenic and must be addressed at the start of treatment. Historically, PTSD was perceived in these ways until quite recently, for example (Najavits et al., 2008). When sequential treatment does occur, the same staff may treat both disorders or the second disorder may be treated after transfer to a different program or facility. For example, a patient with mania and a cocaine use disorder needs mood stabilization before initiating

substance abuse treatment. Conversely, a patient with major depression and alcohol withdrawal delirium is not in a position to discuss treatment adherence to antidepressant medication. Instead, this issue is best addressed when the patient is more stable (i.e., when the delirium has been fully treated and has subsided). Although sequential treatment has the advantage of providing an increased level of attention to the more acute disorder, a typical disadvantage of this model is that patients are often transferred to different clinicians to address the less acute disorder, and the interrelationship between the two disorders may never be adequately addressed.

In *parallel treatment*, both disorders are treated simultaneously, but not by the same treatment team. For example, a patient may receive treatment for an SUD in an addiction treatment program and for a psychiatric disorder in a mental health clinic. Typically, staff members of each program are very well-versed in their own areas of expertise, but not in the other. However, major cross-training efforts relative to co-occurring disorders have improved this situation in the past decade. The different treatment programs may also have different treatment philosophies, which may be confusing to the patient (Mueser et al., 1992; Ridgely et al., 1990). For example, in SUD treatment programs, clinicians may attribute psychiatric symptoms (e.g., depression and anxiety) to substance use; when a patient attempts to obtain relief, the clinician may view this as "drug-seeking" behavior. Alternatively, staff members in psychiatric programs may tend to minimize the importance of substance use and not stress its potential negative consequences.

Unfortunately, patients treated in parallel or sequential programs often have different experiences based on the treatment settings they enter. The two different programs may provide patients with different feedback on the relationship between their substance use and psychological symptoms. Patients in these situations are then left to attempt to integrate these sometimes disparate approaches themselves. In these circumstances, patients may be accused of "manipulating" and "splitting staff" when they present information obtained in one program that is contradictory to another.

In *integrated treatment*, the management of both disorders occurs in one treatment setting, and the same clinician or team of clinicians manages both illnesses. Integrated treatment has become increasingly interesting to researchers and clinicians, fostered by the belief that it is more effective than the other treatment models described earlier.

Integrated Behavioral Therapies for Patients with Co-Occurring Disorders

Integrated psychosocial treatments have been developed for diverse patient populations with co-occurring SUDs and psychiatric disorders, including patients with severe and persistent mental illness (Drake et al., 2001; McHugo et al., 1999), depression (Brown et al., 2006; Lydecker et al., 2010; Cornelius et al., 2011); bipolar disorder (Weiss et al., 2000, 2007, 2009; Weiss & Connery, 2011), personality disorders (Ball, 1998; Linehan et al., 2002), and anxiety disorders such as PTSD (Brady et al., 2001; Najavits et al., 1998; Najavits, 2002; Mills et al., 2012), obsessive–compulsive disorder (Fals-Stewart & Schafer, 1992), social phobia (Randall et al., 2001), and suicidal patients (Esposito-Smythers et al., 2011). We describe here some examples

of the many interventions developed, limiting our discussion to treatments with an evidence base of at least one randomized controlled clinical trial, in an effort to be illustrative rather than comprehensive.

Integrated Group Therapy

Integrated group therapy (IGT) for bipolar disorder and substance abuse, developed by Weiss and Connery (2011) and colleagues (Weiss et al., 2000, 2007, 2009), is a manual-based group psychotherapy based on cognitive-behavioral therapy (CBT) principles, intended for patients with co-occurring bipolar disorder and SUDs, and focused on the relationship between mood symptoms and substance use or abstinence. Arranged around a "central recovery rule" of maintaining abstinence and adherence to prescribed medications, IGT takes into account the essential link between these two behaviors in this traditionally difficult-to-treat population. IGT has had three positive trials, including two randomized controlled trials (RCTs) in which it outperformed standard group drug counseling (Weiss et al., 2000, 2007, 2009); in the most recent study, IGT led to decreased substance use, increased likelihood and rate of achieving abstinence, and increased rates of "good clinical outcome," a composite measure of substance use and mood simultaneously (Weiss et al., 2009).

Seeking Safety

Seeking Safety (SS; Najavits, 2002; Najavits et al., 1998) involves a phase-based framework for PTSD and SUD recovery in which *safety* is defined the first stage of treatment. In SS, safety is the overarching goal: helping clients attain safety in their relationships, thinking, behavior, and emotions. It is a present-focused, CBT approach focused on psychoeducation and coping skills, and designed for flexible use: group or individual format; both genders; all settings (e.g., outpatient, inpatient, residential); all types of trauma and substances; and any clinician. It offers up to 25 topics, each representing a safe coping skill, such as Asking for Help, Compassion, Setting Boundaries in Relationships, Taking Good Care of Yourself, Creating Meaning, Coping with Triggers, Healing from Anger, and Detaching from Emotional Pain (Grounding). The topics can be conducted in any order, using as few or as many as are possible within the available time frame. It strives to be emotionally engaging, with simple, humanistic language, a quotation to start each session, and interactive exercises (for additional details, see the website *www.seekingsafety.org*). SS has had positive outcomes in RCTs including male veterans (Boden et al., 2012) and adolescent girls (Najavits et al., 2006), and is the only model thus far to outperform a control on both PTSD and SUDs (see Najavits & Hien, 2013, for a review of the points covered here). Studies of full-dose SS have shown more positive outcomes than partial-dose SS. The largest study of SS to date was conducted as part of the National Institute on Drug Abuse Clinical Trials Network. That study, despite being a partial-dose of SS (less than half the model) found that at end of treatment SS outperformed the comparison of Women's Health Education (WHE) on therapeutic alliance, HIV risk, and eating disorder symptoms, as well as eight out of nine secondary analyses focused on subsamples of the study (including heavy stimulant users and alcohol

substance abusers) (Ruglass et al., 2012). In main outcomes, PTSD in both SS and WHE patients improved; SUDs improved in neither SS nor WHE, but the study was underpowered to detect SUD outcomes (i.e., over 45% of the sample was abstinent from substances at baseline; Hien et al., 2009). More research is warranted, especially in light of recent consistent results showing that exposure-based PTSD treatment has not outperformed less-intensive controls at end of treatment in four recent RCTs for PTSD–SUD samples (Foa et al., 2013; Mills et al., 2012; Sannibale et al., 2013; van Dam, Ehring, Vedel, & Emmelkamp, 2013; for a summary see Najavits, 2013).

Integrated Dual Disorders Treatment

Integrated dual disorders treatment (IDDT; Drake et al., 2001) focuses on providing mental health and SUD treatment concurrently by a team of interdisciplinary, cross-trained clinicians within the same program. Additional features include assertive community outreach; stagewise interventions that are determined by the client's stage of recovery (engagement, persuasion, active treatment, and relapse prevention); provision of a wide range of ancillary services; time-unlimited services; and motivational interventions. The model has had various positive outcomes for patients with schizophrenia and SUD, when compared to treatment as usual (TAU), for example (Morrens et al., 2011).

Dialectical Behavior Therapy

Dialectical behavior therapy (DBT) is a CBT approach designed for patients with borderline personality disorder. It has four key modules: mindfulness, distress tolerance, emotion regulation, and interpersonal effectiveness. It uses a conceptual approach from applied behavior analysis, "chain analysis," to identify sequential events that form the behavior sequence. It relies on a combination of group therapy, individual therapy, and, for the clinician, peer supervision and support. DBT organizes treatment into stages and targets that are strongly adhered to so as to promote effective outcomes, first addressing behaviors that could lead to the patient's death (e.g., suicide), then behaviors that could lead to premature termination from therapy, then behaviors that destroy the quality of life, and then addressing the need for alternative skills. DBT for substance abusers (Dimeff & Linehan, 2008) is a modified version of DBT for patients with SUDs to promote abstinence and reduce relapse. There have been numerous research studies of DBT, including a meta-analysis that found moderately positive effects for the model; it has been studied in some SUD samples as well, with modest positive results (Linehan et al., 1999, 2002; Harned et al., 2008; Dimeff & Linehan, 2008; see also *www.behavioraltech.org*).

Motivational Interviewing/Motivational Enhancement

Motivational interviewing (MI), developed by Miller and Rollnick (1991, 2002), utilizes theory derived from several psychotherapeutic models: systems, client-centered, CBT, and social psychology. MI is also called "motivational enhancement therapy" (MET), because it is often a brief treatment, conducted in as few as two sessions,

sometimes aimed at helping the patient accept other psychotherapy (e.g., CBT). Guidelines for modifying MI in patients diagnosed with SUDs and psychotic disorders have been published (Carey et al., 2001; Martino et al., 2002). Recent randomized pilot trials of MI in diverse populations with co-occurring disorders suggest that MI may improve the likelihood of making the transition to outpatient treatment (Swanson et al., 1999), improve SUD outcomes (Graeber et al., 2003), and decrease psychiatric hospitalization (Daley & Zuckoff, 1998). A recent review on the application of MI to various mental health disorders co-occurring with SUDs, including anxiety, depression, and eating disorders, suggest promise but also needs further study, with more rigorous scientific testing (Westra et al., 2011). In recent years, too, MET has often been combined with CBT to improve outcomes, including studies addressing comorbidity (e.g., Easton et al., 2012; Cornelius et al., 2011).

Overall Issues in Comorbidity Behavioral Therapies

The past several decades have seen remarkable progress in attending to co-occurring disorders. Various novel and creative approaches have been developed and tested in outcome trials. However, conclusions at this point are mixed and further research is warranted.

First, more research is needed to compare integrated versus single, sequential, or parallel treatment approaches. In general, research on manualized behavioral therapies for SUDs consistently find that they do not outperform each other (Carroll & Rounsaville, 2007; Imel et al., 2008; Sellman, 2010), and certain integrated approaches may not necessarily outperform single-diagnosis approaches (Torchalla et al., 2012; Donald et al., 2005). Yet integrated treatments may have other virtues beyond just outcomes: They may increase engagement, may be perceived as highly relevant, may be easier to implement or teach, or be of lower cost than single, sequential, or parallel approaches.

Second, it is important to note that results have sometimes been surprising. Some studies indicate either no difference in SUD outcomes between co-occurring versus non-co-occurring treatment (e.g., Mills et al., 2012; Schadé et al., 2008; Ball, 2007) or worse outcomes (e.g., Randall et al., 2001). Many factors may play into the heterogeneity of findings, including methodology issues (Horsfall et al., 2009), who conducts the study (e.g., the treatment developer or independent scientists), and the nature of the treatments themselves. More research with high-quality treatments and study designs are needed. Also, there are encouraging new treatment developments, including the burgeoning technology-based approaches, such as computer-delivered care (e.g., Kelly et al., 2012).

SELF-HELP GROUPS AND INDIVIDUALS WITH CO-OCCURRING SUDs AND PSYCHIATRIC DISORDERS

As in other substance-using populations (Miller et al., 1997; Ritsher et al., 2002), self-help group attendance has been associated with improved substance use outcomes

in populations with co-occurring SUDs and psychiatric disorders (Brooks & Penn, 2003; Ritsher et al., 2002). Whether this is a reflection of self-help groups' improving outcomes directly or a self-selection bias (i.e., patients attending self-help groups may be more likely to remain abstinent because they are more motivated) is unclear.

Despite the fact that self-help groups are both free of charge and geographically accessible (Kurtz, 1997), many patients with co-occurring disorders do not attend these meetings (Noordsy et al., 1996). Some clinicians may be reluctant to recommend self-help groups to patients with co-occurring disorders because of concerns that self-help group members might express negative attitudes towards psychotropic medication (Humphreys, 1997). However, recent research indicates that while this sometimes occurs (Noordsy et al., 1996), it is not prevalent (Meissen et al., 1999). Moreover, official Alcoholics Anonymous (AA; 1984) literature states that psychiatric medication, when legitimately prescribed, is appropriate. When educating patients about the interaction between psychiatric symptoms, drug and alcohol use, and medications, clinicians should inform patients that while some self-help group members may criticize the use of medications, this contradicts official AA policy.

Clinicians may also be concerned that these groups only focus on SUDs (Humphreys, 1997) and may therefore not be as helpful to patients who are struggling with other psychiatric disorders. Recent research suggests that some patients and AA contacts (i.e., persons listed in the AA directories as experienced members) agree (Meissen et al., 1999; Noordsy et al., 1996). However, by encouraging patients to focus on obtaining what AA and similar groups offer, and not expecting AA to provide services outside of its stated mission, clinicians can help patients with co-occurring disorders to take advantage of these groups.

To address some of the concerns described earlier, several dual focus self-help groups have emerged for participants with co-occurring SUDs and psychiatric disorders (e.g., Double Trouble in Recovery, Dual Recovery Anonymous, and Dual Disorders Anonymous; Bogenschutz et al., 2006; Magura et al., 2003). Similar to the literature on self-help groups in the SUD population, positive associations have been found between attendance at dual focus self-help groups and abstinence (Magura et al., 2003), as well as psychiatric/quality of life (Magura et al., 2002) outcomes. Again, whether this is a result of self-selection bias regarding the characteristics of patients who attend these meetings is unclear.

General Treatment Themes for Patients with Co-Occurring SUDs and Psychiatric Disorders

Because of the limitations of the empirical literature described earlier regarding psychosocial treatments, it may be helpful to draw on general recommendations provided by various writers on this subject (Bellack & DiClemente, 1999; Carey, 1995; Drake et al., 2001; Drake & Mueser, 2000; Najavits et al., 1996; Rounsaville & Carroll, 1997; Ziedonis et al., 2000; Najavits, 2002; Najavits & Capezza, 2014). Although treatment modalities differ, some common themes can help guide clinicians who must decide how to intervene with their patients. The suggestions are as follows:

- Be empathic and provide support for the difficulty of living with two disorders, but also emphasize accountability (e.g., the presence of a psychiatric disorder is not an excuse to use substances).
- Assist patients in setting a goal to stop substance use. Explore patients' perceptions of the relationship between their substance use and their psychiatric disorders. As part of this process, also explore the longer-term relationship between the two (e.g., an individual may report drinking to reduce social anxiety and initially feel better, then feel worse the following day) and discuss the advantages of a substance-free life.
- Educate patients and their family members about the symptoms of both disorders, and the causal connections between them.
- Monitor symptoms of both disorders and how they interact over time (including the use of biological measures such as urine screens for substance use when indicated).
- Monitor adherence to medications, since nonadherence is a significant risk for relapse.
- To improve functioning and foster the rewards of abstinence, assist patients in developing social, relationship, or vocational skills.
- Attend to patient safety, including attention to the human immunodeficiency virus (HIV) and suicidality, both of which have been found to be increased in patients with co-occurring disorders (Mahler, 1995; Weiss & Hufford, 1999).
- Have available resources to refer patients to self-help groups for each disorder.
- Discuss with patients what to do and whom to call in case of emergency.
- Provide positive reinforcement for improvements, however small, in each disorder.
- For patients who have had significant periods of recovery, acknowledge these successes and, in a positive way, ask them how they accomplished it. Doing so reminds patients of prior successes and can mitigate the feelings of hopelessness and discouragement that often accompany relapse.
- Take a relapse history to help identify triggers to relapse (e.g., discontinuing medications or treatment, engaging in high-risk behaviors such as socializing where alcohol is present).
- Expect occasional breaks in treatment attendance, and engage in active outreach.
- Recognize that patients may be more motivated to work on one disorder than the other, and may need encouragement to attend to both.
- Understand that the clinician too may feel more connection or engagement with one disorder over the other. For example, depression may evoke more sympathy than an SUD.
- Be aware of subtypes and subpopulations even within a particular comorbidity. For example, treatment of depression–SUD comorbidity may differ based on whether psychotic symptoms are present; based on age (e.g., adolescent vs. geriatric), and so forth.
- Provide referral to additional treatments and conduct a thorough assessment of case management needs, including treatment of physical health problems.

PHARMACOTHERAPY FOR PATIENTS WITH CO-OCCURRING SUDs AND OTHER PSYCHIATRIC DISORDERS

The literature regarding when to prescribe pharmacotherapy for patients with co-occurring disorders has evolved considerably in the past 20 years. Previous consensus in the field reflected reluctance to prescribe psychotropic medications in this population, in part based on methodologically flawed studies. For example, older studies examining the use of antidepressants in alcoholics often did not use standardized methods to assess the depressed population, had inadequate dosing or duration of antidepressants, and sometimes measured mood or drinking outcomes, but not both (Ciraulo & Jaffe, 1981). More recently, integrated pharmacological and psychosocial treatments have been increasingly accepted and are now often provided to patients as standard care. However, few trials have integrated novel psychosocial treatments with novel pharmacotherapies, and most treatments instead either focus on new pharmacological or new psychosocial interventions. In spite of this, clinical practice and more recent research have emphasized the importance of integrating pharmacological and psychotherapeutic treatment options.

Major Depression

Multiple meta-analyses of antidepressant medication efficacy in patients with co-occurring depression and SUDs have examined both mood and SUD outcomes (Iovieno et al., 2011; Nunes & Levin, 2004; Torrens et al., 2005). Results have shown mixed efficacy of antidepressants in this population, with better outcomes on depressive measures (comparable to results seen in patients with depression alone) than substance use outcomes, and without clear evidence to suggest use of one particular agent. Studies that required at least 1 week of abstinence before treating the depression yielded larger effect sizes and lower placebo response, suggesting that requiring even 1 week of abstinence before initiating medication treatment can successfully screen out transient depressive symptoms. Studies that exhibited better depression outcomes as a result of antidepressants also showed decreased quantity of substance use, and best outcomes occurred in studies combining antidepressants with psychotherapy. One such study used fluoxetine and CBT in depressed alcoholics, with improved depression and drinking outcomes (Cornelius et al., 1997). In another study, combining sertraline and CBT led to less drinking and improved depression compared to placebo (Moak et al., 2003). One study showed efficacy for desipramine in improving depression scores and length of abstinence from alcohol in a 6-month, double-blind, placebo-controlled trial (Mason et al., 1996). In a single-site trial, Pettinati et al. (2010) found that a combination of sertraline and naltrexone led to improved drinking outcomes and reduced depression compared to either sertraline or naltrexone alone, indicating that this combination may have value for the depressed and actively drinking patient. Most studies examining use of antidepressants in patients with co-occurring depression and cocaine use disorders have shown some effectiveness in antidepressant outcomes but little impact on cocaine use (Torrens et al., 2005). Some evidence suggests that stimulating antidepressants (e.g., tricyclics and bupropion) are preferred for treating depression in the context of cocaine use disorders (Rounsaville,

2004). Although antidepressants have been studied in patients with co-occurring depression and opioid use disorders, mostly in patients receiving methadone maintenance treatment, most studies have shown no improvement in outcomes of either illness (Nunes & Levin, 2004). An exception might be the tricyclic antidepressants imipramine and doxepin, which in this population have shown some benefit in reducing substance use, likely indirectly via positive effects on depression (Nunes et al., 1998; Nunes & Levin, 2004; Titievsky et al., 1982).

Bipolar Disorder

Although face validity would suggest that stabilizing mania or hypomania in patients with bipolar disorder would improve impulse control and judgment, and would therefore lead to decreased substance use, the literature is thin regarding the efficacy of mood-stabilizing medications on bipolar and SUD outcomes. A number of open-label prospective trials using medications for patients with an SUD and a bipolar or bipolar spectrum disorder have been conducted (i.e., with lithium, anticonvulsants, and antipsychotics), with results generally showing improvements in mood symptoms but inconclusive or unclear results regarding SUD outcomes (Brady et al., 1995; Brown et al., 2002, 2003a, 2003b; Calabrese et al., 2001; Gawin & Kleber, 1984; Geller et al., 1998; Nunes et al., 1990). An open-label pilot trial by Gawin and Kleber (1984) indicated that lithium may be effective in reducing cocaine use in patients with cyclothymia and cocaine abuse. However, an open-label trial of lithium in patients with bipolar spectrum disorders and cocaine abuse (Nunes et al., 1990) demonstrated little efficacy in mood or cocaine outcome measures. An open-label trial with valproate in patients with bipolar disorder and an SUD (Brady et al., 1995) resulted in improvement in mood and substance use measures. An open trial of lithium plus valproate in patients with rapid-cycling bipolar I or II disorder and alcohol, cannabis, and/or cocaine dependence (Calabrese et al., 2001) showed improvement in mood symptoms and a 25% remission rate in SUDs after 6 months. Open-label trials of lamotrigine (Brown et al., 2003a) and quetiapine (Brown et al., 2002) in patients with bipolar disorder and cocaine dependence suggest that these medications may be associated with improved mood symptoms and cocaine craving, although not with significant reductions in cocaine use. An add-on RCT of citicoline (Brown et al., 2007) in this same population resulted in decreased cocaine use and no changes in mood. Several double-blind, placebo-controlled studies assessing the efficacy of mood stabilizers or antipsychotic medications in patients with bipolar disorder and SUDs have been conducted (Brady et al., 2002; Brown et al., 2008, 2012; Geller et al., 1998; Salloum et al., 2005). Geller et al. (1998) conducted a double-blind, placebo-controlled, 6-week trial of lithium in adolescents with bipolar disorder and substance dependence, and found lithium to be efficacious for outcomes in both disorders (Geller et al., 1998). Brady et al. (2002) compared carbamazepine in cocaine-dependent individuals with and without a co-occurring affective disorder (note that less than half of the sample with affective disorders had bipolar I disorder, bipolar II disorder, or cyclothymia) in a 12-week, double-blind, placebo-controlled trial. The affective disorder group treated with carbamazepine showed a nonstatistically significant trend toward less cocaine use, while treatment with carbamazepine did not

have any impact on individuals without affective disorders. In a 24-week, double-blind, placebo-controlled trial, Salloum et al. (2005) randomized 59 patients with bipolar disorder and alcohol dependence receiving lithium carbonate and psychosocial interventions to also receive valproate or placebo. Mood symptoms improved in both groups, while patients in the lithium plus valproate group had significantly fewer heavy drinking days. In a 10-week, double-blind, placebo-controlled trial, Brown et al. (2012) compared lamotrigine to placebo in 120 outpatients with bipolar disorder, depressed or mixed mood state, and cocaine dependence. No difference in mood symptoms occurred between the groups, and lamotrigine was associated with a decrease in the amount of money spent on cocaine (though without a significant difference in urine drug screen results). Two double-blind, placebo-controlled trials administering quetiapine to patients with alcohol dependence and bipolar I disorder (treated with mood stabilizers) resulted in no improvement over placebo in measures of alcohol use (Brown et al., 2008; Stedman et al., 2010). Generally speaking, the results of all of these trials confirm the safety and effectiveness of mood stabilizers in improving psychiatric symptoms in patients with co-occurring disorders, but fewer data objectively demonstrate a decrease in substance use, and results of most trials can be seen as preliminary.

Schizophrenia

Most of the literature on the pharmacological treatment of patients with schizophrenia and SUDs is limited to retrospective or open-label prospective studies, often with small sample sizes and/or lacking comparison groups. For example, an open trial of desipramine added to antipsychotic treatment in an integrated dual diagnosis relapse prevention program showed promise in reducing cocaine use and improving psychiatric symptoms (Ziedonis et al., 1992). Two open-label trials have found the first-generation depot antipsychotic flupenthixol deconoate to decrease cocaine (Levin et al., 1998b) and alcohol (Soyka et al., 2003) use in patients diagnosed with schizophrenia and SUDs. Multiple preliminary reports suggest the potential benefit of second-generation antipsychotic medications such as clozapine, olanzapine (Littrell et al., 2001; Smelson et al., 2006), risperidone (Smelson et al., 2002a; Rubio et al., 2006), quetiapine (Brown et al., 2003b), and aripiprazole (Beresford et al., 2005) in improving substance use outcomes in populations with co-occurring schizophrenia, though no conclusive data support the efficacy of first- or second-generation antipsychotic agents over the other (Petrakis, Leslie, et al., 2006; San et al., 2007; Sayers et al., 2005). Generally speaking, the atypical antipsychotic clozapine has shown the most promise in the treatment of patients with schizophrenia and SUDs (Buckley et al., 1994; Drake et al., 2000; Green et al., 2003; San et al., 2007; Lybrand & Caroff, 2009; Zimmet et al., 2000). In one RCT (enrolling 31 patients with co-occurring schizophrenia and cannabis use disorder), clozapine treatment was associated with decreased cannabis use compared to other antipsychotic medications, though without differences in symptoms or functioning (Brunette et al., 2011). The unique pharmacological receptor activity of clozapine may correct underlying reward system deficits of patients with schizophrenia and SUDs (Green et al., 1999, 2008; LeDuc & Mittleman, 1995). Additionally, when administered in low doses (50 mg or

less) to normal volunteers, clozapine has been shown to attenuate the subjective high and rush associated with cocaine, as well as its pressor effect (Farren et al., 2000). In one naturalistic study, Drake et al. (2000) prospectively followed 151 patients with schizophrenia or schizoaffective disorder and co-occurring SUDs for 3 years. At the conclusion of the study, of the 36 patients who received treatment with clozapine, 79% were in remission from alcohol use disorder, compared to only 33.7% of those not taking clozapine. Despite these encouraging findings, evidence from normal study volunteers suggests that low-dose clozapine may increase cocaine blood levels and cause near-syncope (Farren et al., 2000). To our knowledge, however, no case reports or studies have documented clinically significant syncopal episodes in patients with schizophrenia and stimulant use disorders who are prescribed clozapine. Thus, while the introduction of second-generation antipsychotics is encouraging with regard to potential to improve SUD outcomes in this population with co-occurring disorders, well-designed controlled trials are needed to establish safety, tolerability, and efficacy in this population.

Anxiety Disorders

The use of benzodiazepines in populations with SUDs and co-occurring psychiatric disorders is controversial. This issue has been explored almost exclusively in populations with anxiety and alcohol use disorders. The prevalence of benzodiazepine use in patients with alcohol use disorders is greater than in the general population but comparable to that in populations with psychiatric disorders (Ciraulo et al., 1988). Clinicians are often understandably concerned that prescribing benzodiazepines to these patients may lead to either a worsening of the alcohol use disorder, the development of a benzodiazepine use disorder, or potentiation of the benzodiazepine effect when combined with alcohol. Preliminary evidence from case reports (Adinoff, 1992) and a prospective naturalistic study (Mueller et al., 1996) suggests that there may be a carefully selected subpopulation of patients with co-occurring alcohol use and anxiety disorders for whom long-term prescription of benzodiazepine may not affect sobriety or result in benzodiazepine misuse. However, it may not improve outcomes either. For example, a retrospective naturalistic study of veterans with PTSD and SUDs found that physicians were less likely to prescribe benzodiazepines for those with SUDs (Kosten et al., 2000). While those with prescribed benzodiazepines did not have worse outcomes, chronic benzodiazepine treatment (independent of a co-occurring SUD) did not improve anxiety or social functioning in these patients either. Similarly, Brunette et al. (2003) followed SPMI patients with SUDs annually for 6 years and found that the rate of benzodiazepine prescribing was high (up to 43%), but it was not associated with differences in substance use remission, hospitalization, or, interestingly, reductions in anxiety or depression. Also, unsurprisingly, patients prescribed benzodiazepines were more likely to abuse them than those who were not prescribed them. While controlled trials are needed to explore these issues more fully, the findings from these reports add further to concerns that the long-term use of benzodiazepines in these populations perhaps offers the risk of abuse or dependence without great potential for clinical benefit.

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Another pharmacological alternative in this population is buspirone, which does not have abuse potential. Thus far, there have been three double-blind, placebo-controlled studies of buspirone in patients with alcohol dependence and anxiety—either generalized anxiety disorder (GAD; Tollefson et al., 1992), GAD and "other nonpanic anxiety" (Malcolm et al., 1992), or "anxious alcoholism" (Kranzler et al., 1994). Two of the studies found that buspirone was associated with improvements in anxiety and alcohol use outcomes (Kranzler et al., 1994; Tollefson et al., 1992). Although there have been concerns that buspirone's antianxiety effect is more limited in patients with a prior history of benzodiazepine use (Schweizer et al., 1986), a pooled analysis of eight placebo-controlled, randomized trials of patients with GAD (DeMartinis et al., 2000) indicated that patients with either remote (defined as at least 1 month duration) or no prior benzodiazepine treatment experienced improved anxiolysis, fewer adverse events, and clinical improvement similar to that on benzodiazepines compared to patients with recent benzodiazepine treatment. Thus, patients who have not received benzodiazepines for at least 1 month may benefit from buspirone. An RCT of buspirone for patients with co-occurring opioid dependence (on methadone maintenance treatment) and anxiety found that buspirone did not significantly reduce anxiety symptoms, though was associated with trends toward decreased depressive symptoms and slowed relapse rates (McRae et al., 2004).

In patients with co-occurring PTSD and SUDs, one RCT indicated that certain subtypes of patients might benefit from selective serotonin reuptake inhibitor (SSRI) treatment (Brady et al., 2005). In 94 patients with current alcohol dependence and PTSD randomly assigned to receive sertraline or placebo for 12 weeks, those participants with less severe alcohol dependence and earlier-onset PTSD had significantly fewer drinks per drinking day. The SSRI paroxetine has similarly been found to be effective in one randomized, placebo-controlled trial in patients with co-occurring social anxiety disorder and alcohol dependence (Randall, Johnson, et al., 2001). Participants receiving paroxetine showed improvements in anxiety and alcohol dependence symptoms. A follow-up randomized, placebo-controlled trial in patients with co-occurring social anxiety disorder and alcohol dependence (Thomas et al., 2008) found paroxetine to be effective in decreasing social anxiety and self-reported use of alcohol for self-medication purposes (i.e., to cope in order to engage with others in social settings), though it did not correlate with decreases in overall alcohol use.

Attention-Deficit/Hyperactivity Disorder

Although stimulants have been the most extensively studied treatment for adult attention-deficit/hyperactivity disorder (ADHD; Levin et al., 1999), there are concerns that in populations with co-occurring SUDs and psychiatric disorders, they may worsen the course of the SUDs or be subject to abuse themselves (Gawin et al., 1985). At the same time, it has also been observed that a childhood history of ADHD worsens outcomes for cocaine dependence (Carroll & Rounsaville, 1993). Therefore, improving a patient's difficulties with inattention and hyperactivity may have beneficial effects on substance abuse as well (Levin et al., 1999). Consistent with this, prospective studies of children who received stimulant treatment for ADHD indicate

that stimulants have a protective effect against future development of SUDs as an adult (Wilens, 2003; Mannuzza et al., 2003).

Although not as well-studied as stimulants, nonstimulant medications that lack abuse potential are possible alternatives in the treatment of ADHD. In adult populations, bupropion (Wilens et al., 2002) desipramine (Wilens et al., 1996), and atomoxetine (Michelson et al., 2003) have undergone double-blind, placebo-controlled studies and have demonstrated effectiveness in the treatment of hyperactivity and inattention. Little research on these medications, however, has included patients with active SUDs. In one RCT of atomoxetine, adults with ADHD and alcohol abuse or dependence (Wilens et al., 2008) showed clinically significant improvement in ADHD symptoms with atomoxetine compared to placebo, but no difference in time to relapse of heavy drinking. In a single-blind trial of bupropion for adults with ADHD and cocaine abuse (Levin et al., 2002) and an open-label study of venlafaxine, patients with ADHD and alcohol use disorder (Upadhyaya et al., 2001) showed improvements in hyperactivity and inattention, as well as substance use outcomes. In a single-blind trial of sustained-release bupropion, adults with ADHD and SUDs (of all types) showed clinically significant reductions in ADHD symptoms but not SUD markers (Wilens et al., 2010). These results need to be replicated in larger, more rigorous studies.

Clinical trials of methylphenidate in adults with ADHD and a history of cocaine use disorders have also shown promising results. Both open-label trials of long-acting methylphenidate (Castaneda et al., 2000; Levin et al., 1998) and a double-blind, placebo-controlled study of regular methylphenidate (Schubiner et al., 2002) in adults with ADHD and cocaine dependence have all been consistent in that ADHD symptoms improved and no escalation of the stimulant dose was observed. However, while the open trial by Levin et al. (1998a) observed reductions in cocaine craving and use, Schubiner et al. (2002) found no evidence of improved cocaine outcomes in their double-blind, placebo-controlled trial. In a follow-up double-blind, placebo-controlled trial of sustained-release methylphenidate in adults with ADHD and cocaine dependence (all of whom also received weekly individual CBT), Levin et al. (2007) found no difference between methylphenidate and placebo relative to ADHD symptoms (though the majority of both groups showed > 30% improvements in symptoms). Cocaine-positive urine samples, however, decreased significantly in the methylphenidate group, especially among those who also had improvements in ADHD symptoms. In another RCT, Levin et al. (2006) compared sustained-release methylphenidate or sustained-release bupropion to placebo in adults with ADHD and opioid dependence on methadone maintenance; they found no significant differences in ADHD symptoms (with improvement noted in all treatment groups), along with no increase in cocaine use among any groups. In one double-blind, placebo-controlled pilot study of sustained-release methylphenidate, 24 adults with ADHD and amphetamine dependence (abstinent at time of enrollment) showed improvement in self-rated ADHD symptoms in both groups (not statistically different), as well as no differences in drug use, craving for amphetamine, or retention in treatment (Konstenius et al., 2010). In a small crossover trial of sustained release methylphenidate (Szobot et al., 2008), adolescents with ADHD and co-occurring SUDs had more

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improvement in ADHD symptoms than patients receiving placebo. A multisite trial of adolescents with ADHD and SUDs, however, found no more reduction of ADHD or SUD symptoms in those receiving osmotic-release methylphenidate than in those receiving placebo (Riggs et al., 2011). There was no worsening in substance use, however. Despite limited evidence that stimulants may be safely used in this population to treat ADHD without worsening SUD outcomes (and perhaps improving them), their use in these patients remains controversial.

What to Do When the Pharmacological Treatment for the Co-Occurring Psychiatric Disorder Has Abuse Potential

As evidenced in numerous studies, treating a co-occurring psychiatric disorder can often result in positive outcomes in reducing substance use, as well as improvements in the specific psychiatric disorder for which it is prescribed. However, what if the pharmacological treatment has the potential to worsen or create a new SUD? This dilemma is often considered in treating patients with SUDs and co-occurring anxiety disorders or ADHD, when clinicians ask themselves, "Is it safe to prescribe stimulants/benzodiazepines for this patient?"

Pharmacotherapies that do not have abuse potential should be considered first-line treatments before prescribing stimulants or benzodiazepines in these populations (Ciraulo & Nace, 2000; Levin et al., 1999), and it is important that patients receive adequate trials (i.e., dose and duration) of these medications before they are abandoned. Psychosocial treatments with demonstrated efficacy should also be tried before prescribing an abusable medication. For example, CBT has demonstrated efficacy for anxiety disorders (Beck, Wright, Newman, & Liese, 1993) and should be explored before prescribing a benzodiazepine. If these first-line treatments fail to improve the anxiety or ADHD symptoms, then the following guidelines are suggested when prescribing stimulants or benzodiazepines in these patient populations (Ciraulo & Nace, 2000; Levin et al., 1999):

- *Select preparations that limit the potential for abuse.* Medications with longer half-lives or sustained-release preparations have lower abuse potential and are therefore preferable in these populations. Select as low a dose as possible. For benzodiazepines, avoid as-needed-basis prescribing in lieu of a fixed dosing schedule. Limit the number of pills given with each prescription, keep a log of the pills prescribed, and check state-based prescription monitoring programs to minimize potential for doctor shopping (i.e., obtaining prescriptions for controlled substances from multiple providers at the same time). Frequent patient contact can help the clinician assess whether the medication is helpful, as well as whether it is being overused.
- *Use objective measures to document improvements.* For example, using a standardized assessment such as the Adult Behavior Checklist (Murphy & Barkley, 1996) or the Beck Anxiety Inventory (Beck, Epstein, Brown, & Steer, 1988) can help document improvements (or the lack thereof).
- *Monitor substance use.* Patients should be asked about alcohol and drug use,

and other sources of information (urine screens, collateral information from family members) should be strongly considered.

- *Enlist family members' help in supporting and monitoring the patient.* Verify the efficacy and appropriate use of the medication with family members.
- *Patients should safeguard medications.* While the patient may not abuse the medication, family members, roommates, or friends may.
- *Monitor prescriptions.* Keep careful track of the number of pills prescribed, check prescription monitoring programs, and beware of warning signs of abuse such as premature requests for refills, "lost prescriptions," or prescriptions obtained from multiple providers in a short period of time. These usually indicate overuse of the medication.

Pharmacotherapy Targeting Substance Dependence in Populations with Co-Occurring SUDs and Other Psychiatric Disorders

Although pharmacotherapies aimed specifically at decreasing alcohol or drug use (e.g., naltrexone, disulfiram, acamprosate) have been proven and accepted to be efficacious in improving SUD outcomes in non-dually diagnosed populations, their application in populations with co-occurring disorders has lagged behind. Recent data on their safety and potential efficacy in co-occurring populations may be helpful in increasing their use (Petrakis et al., 2005). For example, concerns that disulfiram may cause or exacerbate psychosis (Mueser et al., 2003) has contributed to a reluctance to prescribe it in patients with SPMI (Kingsbury & Salzman, 1990). Published case reports (Brenner et al., 1994), case series (Kofoed et al., 1986; Mueser et al., 2003), and RCTs (Petrakis, Nich, et al., 2006), however, have described its tolerability and potential benefit for improving alcohol outcomes. Additionally, evidence suggests that naltrexone may similarly improve drinking outcomes in patients with alcohol dependence and schizophrenia (Batki et al., 2002; Petrakis et al., 2004), bipolar disorder (Sonne & Brady, 2000; Brown et al., 2009), and major depression (Salloum et al., 1998; Petrakis et al., 2007). In one randomized, placebo-controlled trial, Petrakis et al. (2004) successfully treated 31 patients with schizophrenia and comorbid alcohol abuse or dependence for 12 weeks in an outpatient setting using naltrexone or placebo, in addition to patients' neuroleptic medication. Patients receiving naltrexone had significantly fewer drinking days, less heavy drinking days, and decreased cravings, with no changes in schizophrenia symptoms or status. Additionally, among male military veterans with alcohol dependence and PTSD, naltrexone and disulfiram were found to be more effective than placebo in reducing alcohol consumption (Petrakis, Poling, et al., 2006). Both naltrexone and disulfiram alone were associated with reduced alcohol consumption, though the combination did not confer extra benefit and was associated with more side effects in the PTSD group. Additionally, disulfiram showed more benefit than naltrexone in reducing PTSD symptoms in this study. In a randomized, controlled, 8-week trial of acamprosate in patients with co-occurring alcohol dependence and bipolar disorder (types I and II), acamprosate was well tolerated, without any worsening in depressive or manic symptoms and with some benefit on alcohol outcomes among completers in the last 2 weeks of the trial (Tolliver, Desantis, Brown, Prisciandaro, & Brady, 2012).

FUTURE DIRECT

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FUTURE DIRECTIONS

In the approximately 30 years since researchers and clinicians in the mental health and addictions fields first noted the high prevalence rate of comorbidity and worse outcomes in populations with co-occurring SUDs and psychiatric disorders, important strides have been made in further understanding the epidemiology and sequelae of these disorders, as well as the critical need to develop specific treatments for these populations. Significant progress has been made in developing new treatments, testing them with increasing methodological rigor, and developing optimal treatment methods for these often poorly served patient populations. In the next decade, we are hopeful that this continued research effort will translate into improved treatment methods and outcomes in these patients. Some important future directions include the need for practice guidelines relevant to SUD comorbidity; how to address comorbidity based on different treatment settings (e.g., primary care vs. specialty care); and increased attention to diagnostic decision making when symptom profiles of particular comorbidities overlap (e.g., substance misuse is part of the borderline personality disorder diagnosis). We are hopeful that the next decade will see continued research efforts that will translate into improved clinical care of these patients.

ACKNOWLEDGMENTS

This work was supported by Grant Nos. K24 DA022288 (to Roger D. Weiss), U10 DA15831 (to Roger D. Weiss), and R43DA026649 (to Lisa M. Najavits) from the National Institute on Drug Abuse; Grant Nos. W81XWH-10-2-0173 and W81XWH-10-2-0174 from the Department of Defense (to Lisa M. Najavits); and Department of Veterans Affairs Merit Grant Nos. SPLA-06-S09 and NEUA-001-08S (to Lisa M. Najavits).

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CHAPTER

Gambling D and Other

LIANA R. N. SO
MARC N. POTE
JON E. GRANT

Several behavioral p
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CORE FEATURES

Behavioral and drug ad
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