Treatment of Patients Comorbid for Addiction and Other Psychiatric Disorders

Kathleen T. Brady, MD, PhD, Marcia L. Verduin, MD, and Bryan K. Tolliver, MD, PhD

Corresponding author
Kathleen T. Brady, MD, PhD
Clinical Neuroscience Division, Department of Psychiatry and Behavioral Sciences, Medical University of South Carolina, 67 President Street, Charleston, SC 29425, USA.
E-mail: bradyk@musc.edu

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Psychiatric disorders and drug and alcohol use disorders commonly co-occur. A growing literature has documented the epidemiology and effects on the course of illness of comorbid psychiatric and substance use disorders (SUDs). Advances in treatment of co-occurring illnesses have progressed more slowly. The current article reviews recent developments in the diagnosis and treatment of co-occurring psychiatric disorders and SUDs with particular focus on psychotic disorders, affective disorders, anxiety disorders, personality disorders, and attention-deficit/hyperactivity disorder. Current treatment options and implications for future research are highlighted.

Introduction

Recognition of the prevalence of co-occurring substance use disorders (SUDs) with other psychiatric disorders has grown tremendously over the past 20 years. As awareness of prevalence has increased, the number of studies focusing on various aspects of comorbidity also has increased. These include studies focused on etiologic connections, diagnostic difficulties, consequences, and treatments for individuals with comorbid SUDs and other psychiatric disorders. In this review, we focus on a number of studies published in the last several years that address important issues in the area of comorbidity.

Epidemiology

SUDs and other psychiatric disorders frequently co-occur, with prevalence estimates reported as high as 60% in earlier studies such as the Epidemiological Catchment Area (ECA) study and National Comorbidity Survey (NCS) [1,2]. In the last several years, two large epidemiologic studies, the National Epidemiologic Survey on Alcohol and Related Conditions (NESARC) and the National Comorbidity Survey Replication (NCS-R), have sought to replicate and extend these findings.

The NESARC study reported that 22% of individuals with any mood disorder and 19% of individuals with any anxiety disorder had a co-occurring drug use disorder, with greater comorbidity among women than men [3]. As in both the NCS and ECA studies, comorbidity rates were highest for individuals with bipolar disorder as compared with any other Axis I disorder, with lifetime rates of alcohol and drug use disorders of 58% and 38%, respectively. Diagnoses of panic disorder and social phobia also conferred considerable risk for co-occurring SUD, with 12-month odds ratios of 3.7 and 8.3 for alcohol and other drug dependence, respectively, in panic disorder and 2.3 and 4.6 for alcohol and other drug dependence, respectively, in social phobia.

Similarly, the NCS-R validated the findings of earlier epidemiologic studies and demonstrated that a small number of individuals account for a majority of comorbidity. In particular, more than three fourths of NCS-R diagnoses were given to individuals comorbid for two or more disorders, whereas individuals with three or more disorders accounted for more than one half of diagnoses [4]. Additionally, severity of illness was associated with comorbidity, as a greater percentage of disorders were classified as serious among individuals with three or more diagnoses.

The NCS-R includes a follow-up survey of a subgroup of individuals in the original NCS study. This subgroup contains individuals aged 15 to 24 years at baseline and who participated in follow-up interviews

a decade later. These interviews were conducted in an attempt to determine the extent to which baseline psychiatric disorders predict subsequent transitions to SUDs, and baseline SUDs predict transitions to psychiatric disorders. Most previous research on temporal priority in comorbidity has relied on retrospective self-report concerning relative age of onset of disorders in cross-sectional surveys. This study will be particularly valuable in promoting more in-depth exploration of temporal relationships involving onset, progression, and recovery from psychiatric disorders and SUDs.

Psychotic Disorders

The NCS-R has reported alarmingly high rates of comorbid SUDs in individuals with nonaffective psychotic disorders. The lifetime prevalence rate for any SUD among psychotic individuals was 27%, with a 12-month odds ratio of 22 for drug dependence [5]. Data from the large, multicenter Clinical Antipsychotic Trials of Intervention Effectiveness study found that approximately 60% of the sample used substances, with 37% meeting current criteria for an SUD [6]. Clearly, this comorbidity is highly prevalent and deserving of a dedicated focus in terms of treatment.

A number of studies have suggested preferential use of atypical antipsychotics rather than conventional agents because they have fewer side effects that might compromise compliance, more effectively treat negative symptoms of schizophrenia, and may decrease craving for substances [7]. Although some investigators have reported poor outcomes and/or worsening substance use with typical antipsychotic agents [8], others have not supported this finding [9]. Clozapine is the most-studied agent in this population. In a recent study [10], dually diagnosed schizophrenic individuals were studied prospectively for 10 years in order to examine differential relapse rates with antipsychotic medications. Individuals prescribed clozapine were significantly less likely to relapse to substance use than those who were prescribed other antipsychotic agents (8% vs 40%, $P = 0.003$). However, there is at least one published report of increased cocaine serum levels in individuals treated with clozapine [11]. Evidence supporting the use of other atypical antipsychotics is growing. Smelson et al. [12] found that olanzapine significantly reduced the energy subscale ratings on the Voris Cocaine Craving Scale in a controlled study of cue-elicited craving in 31 individuals with schizophrenia and cocaine dependence. Posthoc analysis of data from a randomized treatment trial demonstrated that dually diagnosed schizophrenic individuals treated with olanzapine had a significantly longer time to treatment discontinuation as compared with those treated with risperidone or typical antipsychotics [12]. In contrast, Sayers et al. [13] found lower cocaine craving with haloperidol as compared with olanzapine in a similar population, and others have reported that individuals with first-episode schizophrenia-related psychosis and an alcohol use disorder (AUD) were less likely to respond to olanzapine than those without an AUD. Another randomized controlled trial assessing olanzapine versus risperidone in the treatment of early psychosis and cannabis use found a greater reduction in cannabis use in the olanzapine group, but no between-group differences in craving, subjective well being, or psychopathology [14].

There are limited data to support the use of other atypical antipsychotic agents. One 12-week, open-label trial found improved substance use and psychiatric outcomes with quetiapine [15], although preliminary reports of intranasal quetiapine abuse may limit its utility in substance-abusing patients [16]. Aripiprazole was reported to reduce alcohol and cocaine craving, as well as to result in fewer positive urine toxicology screens in a small, open-label trial of schizophrenic individuals with cocaine dependence [17]; similar findings have been reported with aripiprazole in bipolar and schizoaffective disorders with co-occurring substance use [18]. Our group recently completed a small, open-label trial of aripiprazole for individuals with co-occurring SUDs and schizophrenia, schizoaffective disorder, or bipolar disorder and found improvements in both psychiatric and substance use outcomes (McRae et al., Unpublished data). Treatment with the long-acting injectable form of risperidone led to improved substance use and psychiatric outcomes, as well as better treatment compliance, as compared with substance-using schizophrenic individuals treated with long-acting injectable zuclopenthixol [19]. Finally, Stuyt et al. [8] conducted a retrospective study of dually diagnosed individuals enrolled in a 90-day inpatient treatment program evaluating differential antipsychotic effectiveness. Patients prescribed risperidone and ziprasidone stayed in treatment for a longer duration than those prescribed olanzapine or typical neuroleptics. The same pattern was true for successful program completion, with 88% and 64% of the risperidone and ziprasidone groups, respectively, completing treatment, as compared with 33% and 40%, respectively, of the olanzapine and typical neuroleptic groups. Further research with more rigorous methodology is needed.

Topiramate augmentation of antipsychotic treatment has been reported effective in reducing alcohol use in a schizophrenic individual in another case report [20]. Whereas initial reports suggested that disulfiram must be used with caution because it may increase central levels of dopamine by blocking dopamine β-hydroxylase and exacerbate psychosis, recent studies have safely investigated its use in severe mental illness and alcoholism. A prospective study evaluating disulfiram and naltrexone alone and in combination versus placebo in alcohol-dependent individuals with psychotic spectrum disorders revealed improved alcohol outcomes with active medication but no between-group differences among the active medication groups [21••]. Another study also found improved alcohol

outcomes with naltrexone as compared with placebo for schizophrenics with alcohol abuse or dependence [22].

The psychotherapeutic management of comorbid schizophrenia and substance abuse is critical. A large randomized trial evaluating a comprehensive treatment program designed for dually diagnosed individuals and involving motivational interviewing, contingency management, and social skills training found the comprehensive treatment to be more effective than a supportive group therapy for both substance use and community-functioning outcomes in individuals with severe mental illness and drug abuse [23••]. Other case management techniques also have been studied. Ries et al. [24] demonstrated in a small, open-label study the feasibility and effectiveness of incorporating management of disability benefits into outpatient psychiatric and substance use treatment programs for dually diagnosed schizophrenics. In contrast, others have reported that having an assigned payee did not reduce substance use [25] but did increase utilization of psychiatric services, suggesting some overall benefit.

Mood Disorders

Bipolar disorder

As previously mentioned, one consistent finding of the large epidemiologic studies conducted to date, including the NCS-R and NESARC, is that bipolar disorder is the Axis I condition most likely to occur with an SUD in adults [1,5,26••]. Recent work has attempted to characterize the comorbidity in terms of temporal order of onset to determine whether it is substance use per se that worsens prognosis, or whether underlying factors may predispose to both substance abuse and poor prognosis. For example, a recent multicenter study found that bipolar patients with a history of comorbid SUDs have lower recovery status, poorer role functioning, and lower quality of life than bipolar patients without substance use history, whether their substance abuse is current or past [27]. Further, the course of bipolar disorder in patients with comorbid AUDs has been shown to differ depending on whether the bipolar disorder or the AUD was antecedent [28]. Patients whose alcoholism preceded the onset of bipolar disorder reportedly are older at the onset of their bipolar illness, recover more quickly from affective episodes, and suffer fewer affective episodes than patients with antecedent bipolar disorder [28]. In contrast, patients with antecedent onset of bipolar disorder were more likely to exhibit symptoms of an AUD at follow-up than those patients with pre-existing alcohol abuse. These findings have been replicated in an analysis of the first 1000 participants in the National Institute of Mental Health-funded, multicenter Systematic Treatment Enhancement for Bipolar Disorder [29]. As the onset of alcohol abuse or dependence in bipolar patients often occurs within 1 year of the first hospitalization for mania [28], clinical recognition of a first manic episode may present an opportunity to prevent SUDs in bipolar patients.

In the first double-blind, placebo-controlled trial comparing valproate plus lithium with placebo plus lithium added to treatment as usual in bipolar individuals with AUDs, Salloum et al. [30••] found a significant reduction in proportion of heavy drinking days, number of drinks per heavy drinking day, and serum biomarker levels of alcohol use in the valproate-treated group. Higher valproate serum concentrations were positively correlated with improved AUD outcomes. Notably, the reduction in drinking occurred in the absence of significant differences in mood stabilization, suggesting that valproate may reduce drinking independent of its efficacy in treating affective symptoms in this population.

Other anticonvulsants recently have been investigated in substance-abusing bipolar patients. Two small, open-label trials evaluating lamotrigine as monotherapy or add-on therapy in individuals with bipolar disorder and cocaine dependence [31] found improvements in mood and decreased cocaine craving but no decrease in cocaine use as assessed by urine testing over a 12-week period. Similarly, a recent open-label trial of lamotrigine in bipolar alcoholics demonstrated improved mood symptoms, as well as decreased craving for alcohol and decreased carbohydrate-deficient transferrin over 12 weeks relative to baseline [32].

Another atypical antipsychotic agent of particular interest in substance-dependent bipolar patients is aripiprazole, a unique dopamine D_2 partial agonist. In the first published trial of this drug in bipolar or schizoaffective individuals with comorbid alcohol dependence, 17 subjects who were switched from their current antipsychotic to aripiprazole reported baseline-to-exit improvements in mood, craving, and alcohol use [18]. In a smaller subset of subjects in this study with cocaine use disorders, aripiprazole was found to reduce cocaine craving but not cocaine use. A recent open-label trial in our laboratory of aripiprazole in substance-abusing patients with bipolar disorder, schizoaffective disorder, or schizophrenia has similarly found a reduction of alcohol and cocaine use by self-report, both in days using and amounts used per day of use [33]. In this study, there was a trend toward greater efficacy in psychiatric and substance use outcomes in schizophrenic/schizoaffective patients relative to bipolar patients, although small sample sizes and differences in dose between groups limit the significance of this result [34].

Pharmacotherapeutic strategies specifically targeting SUDs only recently have been evaluated in patients with comorbid bipolar disorder. For example, no controlled clinical trials of any of the three approved medications for treatment of alcohol dependence have been conducted in bipolar patients, despite the fact that almost one half of all bipolar individuals will develop an AUD at some point in their lives. Brown et al. [35] found significantly decreased craving and days of alcohol use in a 16-week, open-label trial of naltrexone in 34 bipolar, alcohol-dependent patients, suggesting that controlled trials of this medication are warranted. Acamprosate, the most recently approved

medication for alcohol dependence, is currently being tested in an open-label trial at our site, and preliminary results are encouraging. Add-on acamprosate appears to be safe and well tolerated in bipolar patients concurrently taking mood-stabilizing medications; a controlled trial of acamprosate in this population is planned.

In addition to the pharmacotherapy trials discussed previously, a new behavioral therapy recently has been developed and tested in individuals with comorbid SUDs and bipolar disorder. Integrated group therapy (IGT), a manualized cognitive-behavioral therapy (CBT), addresses the similarities between recovery and relapse processes in the two disorders. A recent randomized controlled trial of 20 weeks of IGT versus group drug counseling in substance-dependent bipolar patients concurrently treated with mood stabilizers found higher treatment retention and significantly fewer days of any substance use in IGT-treated subjects relative to controls [36]. The reduction in days of use and in Addiction Severity Index scores was mostly attributable to reduced alcohol rather than other drug intake, and this reduction in drinking persisted over 3 months of follow-up in IGT-treated subjects. The IGT treatment effect on substance use outcomes was not attributable to improved mood outcomes, as IGT-treated subjects actually reported more subsyndromal depressive and manic symptoms during and after treatment. Further study of optimal integration of IGT with pharmacotherapeutic approaches clearly is warranted.

Depression

The association of depression with substance abuse is well established. In NESARC, individuals with major depressive disorder had a lifetime prevalence of 40% for any AUD, and 17% for any drug use disorder [37]. Whether this association is a product of causation, shared etiology, or diagnostic artifacts has been the subject of much debate and continues to influence treatment decisions for patients with both disorders. Attempts to distinguish primary from secondary depression by retrospective assessment of order of illness onset are limited by recall bias or inaccuracy and have yielded inconsistent results. In fact, both SUDs and major depression have been shown to predict the presence of the other disorder at follow-up [38].

Results of controlled trials of antidepressant treatment in substance-dependent patients with major depression have been highly variable [39••]. A recent meta-analysis of controlled trials of antidepressant treatment in substance abusers with unipolar depression found a modest beneficial effect on depressive symptoms [39••]. This analysis included 848 patients from randomized, placebo-controlled, double-blind trials of tricyclic antidepressants ($n = 5$), selective serotonin reuptake inhibitors (SSRIs, $n = 7$), and other classes ($n = 2$). Of the 14 studies included in the analysis, eight were conducted in alcohol-dependent patients; four were conducted in methadone-maintained, opiate-dependent patients; and two recruited cocaine-dependent subjects. The pooled effect size of the antidepressant effect on depression was 0.38 (95% CI = 0.18–0.58). Studies with higher antidepressant effect sizes tended to have low placebo response rates; depression diagnoses after at least a week of abstinence; a lower proportion of women in the sample; no concurrent, manual-guided psychosocial intervention; and employed non-SSRI medications [39••]. The most important predictor of antidepressant benefit in reducing substance use across studies was the size of the antidepressant effect on depression. In studies with depression effect sizes greater than 0.50, the substance effect size was 0.56, whereas among studies with lower depression effect sizes, the antidepressant effect size on substance use outcomes was almost zero. These results suggest that although SUDs need not be a barrier to treatment of depression, antidepressant treatment offers modest benefits and should not be used as a stand-alone treatment for addiction. In a study exploring the efficacy of sertraline for the treatment of depression in methadone-maintained individuals, there was no main effect of sertraline; however, sertraline had significant ameliorative effects on depression for patients who had relatively less environmental adversity [40]. These findings support the impact of contextual factors in moderating the efficacy of medication treatment and the importance of reducing environmental adversity through behavioral intervention in the treatment of individuals with co-occurring disorders.

Post-traumatic stress disorder (PTSD)

There have been several promising recent developments in the area of treatment of co-occurring PTSD and SUDs. In terms of psychotherapeutic treatment, Hien et al. [41] compared the efficacy of a CBT addressing both PTSD and SUD (seeking safety) with a CBT addressing SUD only (relapse prevention) and standard community care in a group of women with co-occurring PTSD and SUD. Both groups receiving CBT experienced greater improvement in both SUD and PTSD symptoms at the 6- and 9-month follow-up; however, there was no evidence for preferential efficacy with the seeking safety intervention.

In a placebo-controlled, double-blind study, the efficacy of sertraline in the treatment of co-occurring PTSD and alcohol dependence was studied. Alcohol use decreased significantly during the trial in both the sertraline and the placebo groups. Cluster analysis revealed significant medication group by cluster interactions for alcohol-related outcomes. Sertraline-treated participants with less severe alcohol dependence and onset of PTSD before age 18 years had significantly fewer drinks per drinking day ($P < 0.001$). For participants with more severe alcohol dependence and later-onset PTSD, the placebo group had significantly greater decreases in drinks per drinking day ($P < 0.01$) and average number of drinks consumed per day ($P < 0.05$). The authors concluded that there are likely to be subtypes of alcohol-dependent

individuals who respond differently to SSRI treatment. Further investigation of differential responders may lead to improvements in the pharmacologic treatment of co-occurring alcohol dependence and PTSD.

As with the other disorders discussed, there has been little investigation of the use of agents approved specifically to treat alcohol dependence in individuals with PTSD. In a 12-week study, Petrakis et al. [42] compared placebo, naltrexone, disulfiram, or a combination in 93 individuals with PTSD. Subjects with PTSD had better alcohol outcomes with active medication (naltrexone, disulfiram, or the combination) than placebo, and overall psychiatric symptoms improved. These results suggest that further exploration of pharmacotherapies targeting alcohol use in comorbid populations is warranted.

Attention-deficit/hyperactivity disorder (ADHD)

Adults with ADHD have higher rates of SUDs as compared with those without ADHD. However, there are few empirical data to inform treatment decisions. In one placebo-controlled, double-blind study, adults with AUDs and co-occurring ADHD were randomly assigned to receive atomoxetine or placebo for 12 weeks [43]. ADHD symptoms were significantly improved in the atomoxetine group ($P < 0.001$). Although analysis of time to relapse showed no significant differences between treatment groups ($P = 0.934$), recurrent event analysis demonstrated that atomoxetine significantly reduced the cumulative number of heavy drinking days (26%) compared with placebo (event ratio = 0.737; $P = 0.0230$). These data suggest that aggressive treatment of ADHD symptoms can be effective in individuals with recent alcohol use and may be associated with improvement in alcohol-related outcomes.

Personality Disorders

Although clinicans have recognized for decades high rates of Axis II pathology among individuals seeking treatment for SUDs, systematic study of this comorbidity is limited. The association of Axis II pathology with SUDs has been confirmed in each of the large epidemiologic studies of substance use comorbidity in samples from the general population. For example, a strong association of antisocial personality disorder (ASPD) with substance abuse was reported in the ECA, NCS, NCS-R, and NESARC studies [1,44,45]. Although not all personality disorders were assessed by any one of these studies, significant SUD comorbidity also was found for borderline [45], as well as histrionic and dependent personality disorder, with many individuals meeting criteria for more than one personality disorder.

ASPD

ASPD is the best studied of all personality disorders with regard to SUDs. In NESARC [44], alcohol dependence was seven to eight times more likely in those with ASPD as compared with those without ASPD, particularly for women (odds ratio = 17 for women). Illicit drug use is even more pervasive, and in NESARC, dependence on drugs other than alcohol was 18.5 times more common in individuals with ASPD relative to the general population.

Both longitudinal and cross-sectional studies have indicated poorer treatment outcomes in individuals with ASPD, including more polysubstance use at follow-up [46], higher likelihood of opiate relapse [47], and overdose [48]. However, using a multipronged treatment approach, Messina et al. [49] found that methadone-maintained patients with ASPD were more likely to abstain from cocaine during treatment than those without ASPD. This was primarily driven by a robust response to contingency management techniques in individuals with ASPD. This promising finding needs to be replicated and expanded.

Conclusions

Recent epidemiologic surveys support prior surveys in finding that SUDs and a variety of psychiatric comorbidities commonly co-occur. The NCS-R has the methodological advantage of providing a 10-year follow-up interview for a subset of individuals who had previously participated in psychiatric interviews for the original NCS. This will be particularly valuable in allowing more in-depth exploration of temporal relationships involving onset, progression, and recovery from psychiatric disorders and SUDs.

In terms of treatment studies for psychotic disorders, there is some evidence that individuals with SUDs have better outcomes when treated with atypical antipsychotics but no clear evidence supporting the use of any particular agent. For bipolar disorder and co-occurring AUD, the well-controlled study indicating that valproate treatment can improve alcohol-related outcomes is informative. For mood and anxiety disorders, SSRIs are likely to be useful for carefully diagnosed patients. However, caution is urged in using SSRIs in patients with early-onset AUDs because a subset of patients may become activated and increase drinking. There also has been progress in exploring behavioral therapies specifically targeting patients with SUDs and psychiatric disorders. Therapies incorporating contingency management into a larger framework of treatment have shown promise in the treatment of co-occurring ASPD and schizophrenia.

Although progress has been made in the recognition and treatment of co-occurring psychiatric disorders and SUDs, much work still must be done, particularly in the area of treatment [50]. Few studies have explored the use of pharmacotherapeutic agents specifically targeting SUDs in individuals with psychiatric disorders. In addition, the application of cognitive and behavioral strategies with proven efficacy in treating individuals with SUDs and psychiatric disorders shows promise and warrants further exploration. Based on what we know now, SUDs should always be specifically addressed in the treatment of all psy-

chiatric disorders, preferably by the same treatment team. Expecting the patient to attend both a psychiatric clinic and a substance abuse clinic is not likely to be effective. This means that all psychiatrists should be trained in the treatment of SUDS, because they so commonly occur in the practice of psychiatry.

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