

Treatments for Patients With Dual Diagnosis: A Review

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Background: Comorbid substance use and mental illness is prevalent and often results in serious consequences. However, little is known about the efficacy of treatments for patients with dual diagnosis.

Methods: This paper reviews both the psychosocial and medication treatments for those diagnosed with a substance-related disorder and one of the following disorders: (a) depression, (b) anxiety disorder, (c) schizophrenia, (d) bipolar disorder, (e) severe mental illness, and (f) nonspecific mental illness. We made no restriction of study design to include all published studies, due to the dearth of studies on treatments of patients with dual diagnosis.

Results: Fifty-nine studies were identified (36 randomized-controlled trials; RCT). Limited number of studies, especially RCTs, have been conducted within each comorbid category. This review did not find treatments that had been replicated and consistently showed clear advantages over comparison condition for both substance-related and other psychiatric outcomes.

Conclusions: Although no treatment was identified as efficacious for both psychiatric disorders and substance-related disorder, this review finds: (1) existing efficacious treatments for reducing psychiatric symptoms also tend to work in dual-diagnosis patients, (2) existing efficacious treatments for reducing substance use also decrease substance use in dually diagnosed patients, and (3) the efficacy of integrated treatment is still unclear. This review provides a critique of the current state of the literature, identifies the directions for future research on treatment of dual-diagnosis individuals, and calls for urgent attention by researchers and funding agencies to conduct more and more methodologically rigorous research in this area.

Key Words: Dual Diagnosis, Treatment Efficacy, Alcohol and Drug Abuse, Psychiatric Disorders.

SUBSTANCE USE AND mental illness often result in serious consequences, not only to those who have them but also for the family and society. For example, Murray and Lopez (1996) found that mental health disorders accounted for 5 of the 10 most burdensome diseases in the world in 1990. These included major depressive disorder, alcohol-related disorder, bipolar disorder, schizophrenia, and obsessive-compulsive disorder. Drug and alcohol-related disorders were estimated to cost the United States over \$360 billion [\$180.9 billion for drug in 2002 (Office of National Drug Control Policy, 2004) and

\$184.6 billion for alcohol in 1998 (US Department of Health and Human Services, 2000)]. Although these studies point to the impact of these conditions, they fail to point out that mental illness and substance abuse frequently co-occur.

The prevalence of substance-related disorders among those with another psychiatric diagnosis is notable. Research suggests that among individuals diagnosed with a lifetime schizophrenia disorder, between 33% and 66% meet criteria for at least one substance-related disorder in their lifetime (Alterman et al., 1982; Barbee et al., 1989; Mueser et al., 1992; Regier et al., 1990). For example, the Epidemiologic Catchment Area (ECA) study, which involved administration of the Structured Diagnostic Interview Schedule to 20,291 community-dwelling and institutionalized adults over the age of 18 years, found that over 56% of persons with any lifetime bipolar disorder and 47% of persons with a lifetime schizophrenia also had a comorbid substance-related disorder in their lifetime (Regier et al., 1990).

Similarly, individuals diagnosed with substance use disorders (SUDs) often have comorbid psychiatric disorders. The ECA study estimates that about one-third (37%) of individuals with lifetime alcohol-related disorders and about one-half (53%) of individuals with lifetime drug-related disorders have a lifetime comorbidity of another psychiatric diagnosis (Regier et al., 1990). Among

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treatment seekers with any alcohol-related disorder, over 40% had a comorbid mood disorder and 33% had an anxiety disorder; among treatment seekers with drug-related disorder, over 60% had a comorbid mood disorder and over 42% had an anxiety disorder (Grant et al., 2004).

Disease-specific treatments have been shown to be efficacious for individuals diagnosed with substance use or other psychiatric disorders alone (e.g., Craighead et al., 1998; Finney et al., 1999; Weissman and Markowitz, 2002). While a number of theoretical models have been developed to explain the onset and maintenance of comorbidity (see Mueser et al., 1998; Verheul and van den Brink, 2005), there are still little data supporting one model over another. However, in the most simplistic, albeit useful sense, existing efficacious treatments that successfully reduce psychiatric symptoms in patients with psychiatric symptoms alone should also reduce psychiatric symptoms in patients with both psychiatric disorders and SUDs. Similarly, one would expect that treatments that successfully reduce substance use in patients with SUDs alone should also reduce substance use in patients with SUDs and psychiatric disorders (e.g., Hien et al., 2004). Of course, situational and disease-specific factors may act to moderate these expectations. For example, patients with dual diagnoses may be more disturbed, have more severe symptoms generally, and may be less compliant in coming to treatment and taking medications (Soyka, 2000; Soyka et al., 2001).

Also, one might expect that a treatment targeted to reduce a psychiatric symptom (e.g., depression) could also reduce substance use, in that substance use could be secondary to depression (e.g., for "self medication" purposes). Similarly, a treatment that is targeted to reduce substance use could perhaps also reduce psychiatric symptoms (e.g., depression as the consequence of alcohol use). However, a multimodel, multicomponent treatment, such as most of the integrated treatment programs described in this paper, could in fact target both substance use and psychiatric symptoms or, even if they primarily target one type of problem rather than the other, could "spill over" and affect symptoms more generally.

Previous literature has noted the need to evaluate and summarize the efficacy of treatments for dual diagnosis. For example, Nunes and Levin (2004) conducted a meta-analysis on the use of medications to reduce depressive symptoms in individuals with alcohol or other drug dependence. These authors conclude that antidepressants are effective for reducing depressive symptoms among dually diagnosed patients, although the effect of these medications on substance use is limited. However, rigorous evaluations of the efficacy of treatments for other forms of dual diagnosis are lacking in the literature. Indeed, Watkins et al. (2005) reviewed treatment recommendations for persons with co-occurring affective or anxiety and SUD and concluded that there is a lack of evidence for most recommendations, with most treatment

recommendations made by expert opinion only. Other committees, such as the Depression and Bipolar Support Alliance (DBSA), reviewed existing literature on treatments for individuals with SUDs and either major depression or bipolar disorder and concluded that medication, psychosocial, and self-help treatments are available and show some evidence of effectiveness, but suggest that more evidence is needed to demonstrate efficacious treatment effects for these classes of dual diagnosis (O'Brien et al., 2004).

Understanding the need to evaluate the existing evidence for the efficacy of treatments for a broad range of dual-diagnosis categories, the goal of this paper is to review the current scientific literature on the treatments for individuals diagnosed with co-occurring substance use and psychiatric disorders, evaluate the methodological issues of published studies, and describe what still needs to be done to develop and evaluate treatments for those who have dual disorders. The existence of both a current substance-related disorder and another psychiatric disorder is termed "dual diagnosis" in this paper. Within this context, a current psychiatric disorder may consist of both DSM-IV Axis I and Axis II diagnoses. Indeed, Verheul and van den Brink (2005) report potential mechanisms relating substance abuse to Axis II disorders. However, because there is a dearth of intervention studies examining treatment for patients with the latter category of dual diagnosis, our review only focuses on treatment for patients with Axis I dual diagnosis categories. Effect size estimates are calculated to provide information on treatment effect. However, we have elected not to conduct a meta-analysis due to the dearth of studies in many areas and the great heterogeneity of dual-diagnosis categories reviewed.

MATERIALS AND METHODS

We surveyed MEDLINE and PsychInfo for empirical studies on the treatment of individuals with dual diagnosis. Because dual diagnosis encompasses many diagnostic categories, an extensive list of search terms was used, including dual diagnosis, comorbid, treatment, intervention, therapy, depression, anxiety, schizophrenia, psychotic/psychosis, severe mental illness, alcohol, drug, and substance. In an effort to locate articles not found in our keyword search, reference sections of published articles were also examined. Studies included in this review are those published in English since 1980. We made no restriction of study design to include all published studies, due to the dearth of studies on treatment of dual diagnosis. No quality rating of the studies was attempted. When studies made a distinction between "primary" versus "secondary" to other psychiatric disorders (symptoms developing during or within 1 month of substance intoxication or withdrawal), such distinctions were noted throughout.

Estimating Treatment Effects

We calculated effect sizes (Cohen's *d*) for the main psychiatric and substance use outcomes within each study. In cases where multiple follow-up assessments were conducted, only measures taken most recently posttreatment were used to compute effect sizes. Cohen's *d* (1977) indicates the standardized mean difference between the treat-

ment and comparison condition, with an effect of 1.0 indicating that the mean score on an outcome for the treatment condition differed by 1 standard deviation compared with the mean score for the comparison condition. In this paper, the sign of the effect size is always reported to demonstrate lower levels of symptomatology (e.g., depressive symptoms, drug use) in the treatment condition than the comparison condition. Cohen's (1977) benchmarks for small (0.2), medium (0.5), and large (0.8) effect sizes were used. Where possible, we converted chi-square statistics to Cohen's d (Cohen, 1977) for studies utilizing categorical outcomes. In "Results," we describe all differences that appeared to be potentially clinically meaningful (i.e., effect size 0.3 and above) and p -values are also offered for readers to determine the likelihood of type 2 error. Occasionally, researchers described a measure but did not report findings for it or reported results only as nonsignificant. In these situations, an exact effect size could not be calculated.

RESULTS

A total of 59 studies met the above criteria. The studies are grouped below according to the specific category of mental illness (e.g., depression, anxiety) and, where appropriate, specific drug (e.g., alcohol) and treatment (e.g., psychosocial, medication) categories.

Treatments for Substance-Related Disorders and Comorbid Depression

Alcohol-Related Disorders and Depression

Psychosocial Treatments. There are a substantial number of studies examining treatments for depression or alcohol-related disorders separately. For example, interpersonal psychotherapy (IPT; Weissman and Markowitz, 2002) and cognitive and behavioral interventions (cognitive-behavioral therapy; CBT; Craighead et al., 1998) have demonstrated efficacy with depressive disorders; CBT, 12-step, and relapse prevention have been shown to be efficacious in the treatment of alcoholism (e.g., Finney et al., 1999; Irvin et al., 1999; Project Match Research Group, 1997, 1998). However, few studies have examined treatments for patients with depression and a comorbid alcohol-related disorder. Only 1 psychosocial treatment study was identified.

Brown et al. (1997) compared an 8-session CBT for depression (CBT-D) with a Relaxation Training Control condition (RTC) plus standard alcohol treatment for patients with alcohol dependence and elevated depressive symptoms [Beck Depressive Inventory (BDI) score > 9]. Participants in the CBT-D condition showed significant improvements in depressive symptoms [i.e., Hamilton Depression (HAM-D) and Profile of Mood States (POMS) depression subscale] during treatment compared with those in the RTC condition (see Table 1), with an average effect size of 0.85. Participants receiving CBT-D also had significantly better alcohol use outcomes on total abstinence, percent day abstinence, and drinks per day between the 3- and 6-month follow-ups. Furthermore, changes in depressive symptoms mediated changes in the

number of drinks consumed per day and partially mediated changes in percent days abstinent.

Medication Treatments. We found 11 randomized-controlled trials (RCTs) examining the efficacy of psychotropic medications for depression and alcohol-related disorders, with 3 additional non-RCT studies (see Table 1). Of the random-design studies, 2 examined tricyclic antidepressants (TCAs), with both demonstrating significant improvements in depressive symptoms (effect sizes in the medium to large range). Drinking outcomes for these 2 studies were mixed. One study found an advantage for desipramine over placebo on drinking outcomes, whereas the other found that imipramine+relapse prevention did not add any benefits on drinking outcomes to relapse prevention alone. Selective Serotonin Reuptake Inhibitors (SSRIs) and atypical antidepressants showed mixed results for both depression and alcohol-related outcomes.

Tricyclic Antidepressants. McGrath et al. (1996) conducted a 12-week placebo-controlled trial of imipramine (150–300 mg) for individuals meeting DSM-III-R criteria for alcohol dependence/abuse and a primary depressive disorder (major depressive disorder, dysthymia, or depressive disorder NOS). In addition to medication (or placebo), participants received weekly individual relapse prevention. Participants receiving imipramine+relapse prevention were more likely to demonstrate improvement at 12 weeks in depression (Cohen's $d = 0.40$) but not alcohol use, compared with participants receiving placebo+relapse prevention.

Mason et al. (1996) conducted a randomized, double-blind, placebo-controlled trial of desipramine for 6 months on 71 participants with primary alcohol dependence, abstinent for 8 days, with stratified randomization on the presence ($n = 28$) or absence ($n = 43$) of secondary depression. Participants who received desipramine had significantly decreased HAM-D scores compared with those who received placebo (Cohen's $d = 0.93$). Although the advantage of desipramine over placebo for drinking outcomes did not reach statistical significance, the effect size was in the medium to large range ($d = 0.65$), with a 74% likelihood that participants receiving desipramine had better drinking outcomes than those receiving placebo.

In an open-label study, Nunes et al. (1993) tested imipramine on 60 patients who met DSM-III-R criteria for primary major depressive disorder or dysthymia and alcohol abuse/dependence. Twenty-seven (45%) participants were considered to be responders, with mean posttreatment HAM-D scores of 3, and 18 patients were abstinent and 9 continued to drink at a much reduced level.

Selective Serotonin Reuptake Inhibitor. Roy (1998) studied 36 participants meeting DSM-III-R criteria for current major depression and alcohol dependence who were abstinent for 2 weeks in a 6-week randomized double-blind controlled trial. Compared with those receiving placebo, participants receiving sertraline (100 mg) showed

Table 1. Outcomes of Treatments for Individuals with Alcohol-Related Disorder and Comorbid Depressive Disorder

Source	Interventions	Group n	Randomized Design	Initial Abstinence	Alcohol- Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Alcohol-Related Outcomes Effect Sizes (Cohen's <i>d</i>)
<i>Psychosocial Interventions</i>									
Brown et al. (1997)	(T) Cognitive-Behavior Therapy (CBT)	19	No	Yes	DSM-III-R Alcohol dependence	BDI > 9	8 sessions, 45-minutes each	(1) HAM-D* 0.69 (2) POMS Depression* 1.02 (3) POMS Anxiety* 0.83	(1) Percent days abstinent 0.59 (2) Drinks per day* 0.71
	(C) Relaxation training (RT)	16							
TCAs	McGrath et al. (1996)	(T) Imipramine 300 mg/d+relapse prevention	36	Yes	No	DSM-III-R Alcohol dependence	12 weeks	(1) HAM-D* 0.40	(1) % days drinking 0.08 (2) % days drinking heavily 0.26
		(C) Placebo+relapse prevention	33						
Mason et al. (1996)	(T) Desipramine 200 mg/d	15	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD	26 weeks	(1) HAM-D* 0.93	(1) Days to relapse 0.65
Nunes et al. (1993)	(C) Placebo	13							
	(T) Imipramine	60	No	No	DSM-III-R Alcohol abuse or dependence	DSM-III-R Major MDD or Dysthymia	12 weeks	Of all participants, 27 (45%) were deemed "responders". Mean post-treatment HAM-D = 3 (+/-3).	Of 27 responders, 18 achieved abstinence and 9 had significant reduction in alcohol use
	(C) No control								
<i>SSRIs</i>									
Roy (1998)	(T) Sertraline 100 mg/d	18	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD	6 weeks	(1) HAM-D* 1.06 (2) BDI* 0.76	Not Tested
	(C) Placebo	18							
Pettinati et al. (2001)	(T) Sertraline 200 mg/d	12	Yes	No	DSM-III-R Alcohol dependence	DSM-III-R MDD or DD	14 weeks	(1) HAM-D -0.21 (2) BDI -0.20	(1) Percent Days Drinking 0.10 (2) Weeks to relapse -0.10
	(C) Placebo	17							
Gual et al. (2003)	(T) Sertraline 50-150 mg/d	39	Yes	Yes	DSM-IV Alcohol dependence	DSM-IV MDD, DD, or Both	24 weeks	(1) HAM-D NC (2) SF-36 Mental Health 0.48	(1) Days to Relapse -0.17 (2) Cumulative Days of Abstinence 0.10
	(C) Placebo	44							
Moak et al. (2003)	(T) Sertraline 200 mg/d+CBT	38	Yes	Yes	DSM-III-R Alcohol dependence or Abuse	DSM-III-R MDD or Dysthymia	12 Weeks	Females HAM-D* 0.76 Males BDI* 1.09 HAM-D 0.01	(1) Time to first heavy drinking day NC (2) Time to first drink 0.50 (3) Drinks per Drinking Day* 0.50 (4) Percent Days Abstinent 0.02
	(C) CBT +placebo	44							
Cornelius et al. (1997)	(T) Fluoxetine 25 mg/d	25	Yes	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD	12 weeks	HAM-D* 0.57 BDI 0.45	(1) Cumulative Drinks* 0.76 (2) Cumulative drinking days* 0.57 (3) Drinks per drinking day* 0.68
	(C) Placebo	26							
Oslin (2005)	(T) Naltrexone (50 mg/d)+sertraline	Yes	Yes	Yes	DSM-IV Alcohol dependence	(1) Depression Remission (HAM-D < 10)	12 weeks	(1) Depression Remission (HAM-D < 10) -0.09	(1) Abstinence from Heavy Drinking -0.10

Author (Year)	Treatment	N	Alcohol dependence	DD	DSM-III-R	DSM-III-R	DSM-III-R	DSM-III-R	Outcome	Effect Size
Atypical Antidepressants	(100 mg/d) + supportive Therapy	37								
	(C) Placebo + sertraline (100 mg/d) + supportive therapy	37	No	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD	12 weeks	HAM-D (<8)*	(1) Drinks per day (2) Alcohol Craving	0.08 0.38
	(T) Nefazadone 500 mg/d + CBT	32	No	Yes	DSM-III-R Alcohol dependence	DSM-III-R MDD	12 weeks	HAM-D (<8)*	(1) Drinks per day (2) Alcohol Craving	0.08 0.38
	(C) Placebo + CBT	32	Yes	Yes	DSM-IV Alcohol dependence	DSM-IV MDD	10 weeks	(1) HAM-D (2) State Anxiety Inventory	(1) Drinks per week* (2) Heavy drinking days*	0.82 1.01
Brown et al. (2003)	(T) Nefazadone 400 mg/d + supportive psychotherapy	21	Yes	No	DSM-IV Alcohol dependence	DSM-IV MDD	12 weeks	(1) 45% reduction in HAM-D scores (2) 40% reduction in HAM-A scores	(1) 27.5% reduction in Alcohol craving (2) 87% reduction in drinks per week (3) 68% reduction in days drinking per week	
	(C) Placebo + supportive psychotherapy	20	No	No	DSM-IV Alcohol dependence	DSM-IV MDD	12 weeks	(1) 45% reduction in HAM-D scores (2) 40% reduction in HAM-A scores	(1) 27.5% reduction in Alcohol craving (2) 87% reduction in drinks per week (3) 68% reduction in days drinking per week	
	(T) Nefazadone 600 mg/d	13	No	No	DSM-IV Alcohol dependence	DSM-IV MDD	12 weeks	(1) 45% reduction in HAM-D scores (2) 40% reduction in HAM-A scores	(1) 27.5% reduction in Alcohol craving (2) 87% reduction in drinks per week (3) 68% reduction in days drinking per week	
Other Medications	(C) None									
	(T) Lithium, 600–1,200 mg/d	89	Yes	Yes	DSM-III Alcohol dependence	DSM-III MDD or DD	52 weeks	(1) BDI	(1) Days drinking past 4 weeks (2) Addiction Severity Index Global	0.24 – 0.11
Salloum et al. (1998)	(C) Placebo	82	Yes	No	DSM-III Alcohol dependence	DSM-III MDD	12 weeks	Trend in reduction of HAM-D scores (p = .078), BDI scores (p = .071), and GAF scores (p = .076)	Significant reduction in drinks per week and urge to drink	
	(T) Naltrexone, 50 mg/d	18	Yes	No	DSM-III Alcohol dependence	DSM-III MDD	12 weeks	Trend in reduction of HAM-D scores (p = .078), BDI scores (p = .071), and GAF scores (p = .076)	Significant reduction in drinks per week and urge to drink	

T, Treatment Condition; C, Comparison Condition; MDD, Major Depressive Disorder; DD, Dysthymic Disorder; NC, Not calculable; HAM-D, Hamilton Depression scale; HAM-A, Hamilton Anxiety scale; BDI, Beck Depressive Inventory.

*Significant difference (p < .05).

Initial Abstinence = Yes if patients were abstinent before beginning treatment.

Cohen's d represents effect of treatment condition (C) relative to control condition (T) with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

significant improvement in depressive symptoms, as indicated by both HAM-D and BDI scores (Cohen's $d = 1.06$ and 0.76 , respectively). Similarly, a greater percentage of participants receiving sertraline demonstrated a 50% reduction in HAM-D or BDI scores (22% and 67%, respectively). Alcohol outcomes were not examined.

Pettinati et al. (2001) conducted a double-blind clinical trial of sertraline for individuals with a DSM-III-R diagnosis of major depression and comorbid alcohol dependence. Participants were randomly assigned to receive either 200 mg/d of sertraline ($n = 12$) or placebo ($n = 17$) for 14 weeks. Drinking outcomes and depressive symptoms did not differ between the sertraline and the control groups.

In a 24-week double-blind, placebo-controlled, randomized clinical trial conducted in Spain, Gual et al. (2003) enrolled 83 depressed, recently detoxified alcohol-dependent patients to compare sertraline (50–150 mg) with a placebo. No significant differences were observed between sertraline and placebo groups on depressive or drinking outcomes.

Moak et al. (2003) randomized 82 individuals diagnosed with both primary major depressive disorder and concurrent alcohol abuse or dependence to receive sertraline (200 mg)+CBT ($n = 38$) or placebo+CBT ($n = 44$) for 12 weeks. Female participants who received sertraline+CBT ($n = 15$) had lower HAM-D and BDI scores at follow-up compared with those receiving placebo+CBT ($n = 17$; Cohen's $d = 0.76$ and 1.09 , respectively). No difference was observed for male participants, but the interaction effects between gender and treatment were not examined. In addition, participants receiving sertraline+CBT reported less drinks per drinking day than those who received placebo (Cohen's $d = 0.50$), but no differences were observed in the 2 groups in days to first drink, days to first heavy drinking day, percent days abstinent, or heavy drinking days per week.

In a 12-week randomized trial, Cornelius et al. (1997) compared fluoxetine (20–40 mg) with placebo in 51 alcoholic patients with primary depressive disorder. Participants receiving fluoxetine ($n = 25$) showed significantly greater improvement in HAM-D scores than those receiving placebo ($n = 26$; Cohen's $d = 0.57$). Beck Depressive Inventory scores, however, were not significantly different between the 2 conditions (Cohen's $d = 0.45$). Drinking outcomes showed significant advantages for those receiving fluoxetine, including total alcohol consumption, cumulative number of drinking days, number of drinks per drinking day, and number of days of heavy drinking.

Oslin (2005) conducted a 12-week trial examining the efficacy of naltrexone and sertraline to that of a placebo and sertraline in a sample of 74 older adults with DSM-IV diagnoses of both alcohol dependence and either substance-induced or primary depressive disorder. Participants randomized to the experimental condition ($n = 37$) received 50 mg/d of naltrexone for alcohol dependence and

100 mg/d of sertraline for depression. Participants randomized to the control condition ($n = 37$) received a placebo and 100 mg/d of sertraline. Beyond medication prescription, all participants in the trial received 10 sessions of supportive therapy. Primary outcomes were depression remission (< 10 on HAM-D) and relapse to heavy drinking (> 4 standard drinks/d for men; > 3 for women). The results indicated no difference in outcomes for the 2 treatment conditions, with 66% of patients having a favorable alcohol response (i.e., no relapse) and approximately 53% had a remission from depression.

Atypical Antidepressants. In a double-blind, placebo-controlled trial, Roy-Byrne et al. (2000) randomized 64 individuals with DSM-III-R diagnoses of primary major depression and alcohol dependence to receive either 12 weeks of Nefazadone (500 mg) or placebo. In addition to receiving medication or placebo, all participants received cognitive-behavioral skills training group therapy once per week. Participants receiving nefazadone were more likely to have a "full response" (HAM-D < 8) in depression by the 12th week than those receiving placebo (48 and 16%, respectively; Cohen's $d = 0.71$). There were no significant differences between groups in alcohol consumption (Cohen's $d = .08$) and craving (Cohen's $d = 0.38$).

Hernandez-Avila et al. (2004) examined the efficacy of nefazodone (600 mg) for comorbid alcohol dependence and major depression in a 10-week randomized-controlled trial. Compared with the control group ($n = 20$), participants receiving nefazodone ($n = 21$) showed significant reduction in drinks per week ($d = 0.82$) and heavy drinking days ($d = 1.01$), but did not improve in depressive symptoms. The authors attributed the lack of significant effects to limited statistical power. However, we calculated the effect size on depressive symptoms to be very small (Cohen's $d = .07$).

Brown et al. (2003) conducted an open-label trial of nefazodone for patients diagnosed with major depressive disorder and alcohol dependence ($N = 13$). All participants met DSM-IV diagnosis for both disorders and scored 18 or higher on the HAM-D. Outcomes included the HAM-D, Hamilton Anxiety (HAM-A), and a modified version of the Cocaine Craving Questionnaire for alcohol use. Participants began treatment, receiving 100 mg/b.i.d. of nefazodone and were titrated to 300 mg/b.i.d. The results demonstrated significant improvement over a 12-week period in all outcome measures.

Other Medications. In addition to antidepressants, other medications have also been tested with depressed alcoholic patients. Alcoholic patients, with or without depression, were randomized to receive either lithium or placebo (Dorus et al., 1989). No significant difference was found between the 2 groups on many depressive and alcohol outcome measures.

In a pilot study, 18 participants meeting DSM-III-R criteria for major depression and alcohol dependence

received naltrexone (50 mg) for 12 weeks, with no control condition (Salloum et al., 1998). Participants demonstrated significant decreases in the number of weekly alcohol drinks and their urge to drink alcohol when triggered, and no differences on their BDI or HAM-D scores.

Drug-Related Disorders and Depression. We found only 1 noncomparative study examining the efficacy of a psychosocial intervention in treating depressed drug users. One study (Nunes et al., 1998) showed that participants receiving imipramine (a TCA)+methadone had better depressive and substance use outcomes than those receiving methadone alone. Three additional studies examined SSRIs (i.e., fluoxetine or sertraline), and did not show a favorable depression or substance-use response (see Table 2).

Psychosocial Treatment. Charney et al. (2001) provided an integrated intervention to 43 patients seeking treatment for substance-related disorders who also had significant depressive symptoms (no control comparison). Patients' substance use decreased by 31.5%. The average BDI scores reduced from 26.4 to 12.7, and HAM-D scores decreased from 23.3 to 13.6.

Medication Treatments. In a randomized placebo-controlled study of imipramine (TCA), Nunes et al. (1998) enrolled 137 opiate-dependent participants with a comorbid depressive disorder (i.e., major depression, dystymia, or depression NOS). In addition to imipramine (maximum dose = 300 mg) or placebo, all patients received methadone for opiate dependence. Participants receiving imipramine had significantly lower depression scores (HAM-D; $d=0.68$) and reported fewer days per week using any substance ($d=0.51$) than those receiving placebo by the 12 weeks. However, few participants in either condition achieved abstinence, and no differences were observed in heroin or cocaine use over the 12-week period. Of particular note in this study, change in depression was found to mediate the relationship between treatment and substance use.

Petrakis et al. (1998) conducted a 12-week, double-blind, placebo-controlled trial of fluoxetine (SSRI; 60 mg) for 44 opioid-dependent individuals with a comorbid primary or substance-induced depressive disorder and either an HDRS score of 15 or above or a BDI score of at least 9. Outcomes included both the BDI and HAM-D for psychiatric symptoms, and the anxiety sensitivity index (ASI) for cocaine and heroin use. The results indicated no differences between placebo and fluoxetine conditions on depressive outcomes. Similarly, no significant differences in drug use were observed between treatment conditions, although effect sizes favored fluoxetine (Cohen's $d=0.22-0.50$).

In another double-blind, placebo-controlled trial of fluoxetine, Schmitz et al. (2001) evaluated 68 cocaine-dependent patients with major depressive disorder. Participants were randomized to receive either 40 mg/d of fluoxetine or placebo for a total of 12 weeks. In addition, all participants received 24 sessions of CBT integrating

relapse prevention and self-control therapy. Depressive symptoms improved equally for participants in both conditions. Cocaine use for participants in the placebo condition was significantly less than those in the fluoxetine condition at 6 weeks, but this difference did not persist through the end of treatment.

Carpenter et al. (2004) examined the efficacy of sertraline (SSRI; 200 mg) versus placebo for depressed, opiate-dependent individuals and the moderating effect of both negative and positive environmental circumstances. The depressive disorders had to be either primary, persistent, or at least of a 3-month duration in the current episode. Negative environment included negative or aversive consequences in work, family and friend, legal, and substance abuse domains; the positive environment domain included work patterns, current living situation, close friendships, and use of spare time. There was no main effect of sertraline on either depression or substance use outcomes, but the results indicated an interaction effect, such that the efficacy of sertraline for reducing depressive symptoms (HAM-D score) depended on environmental factors. Participants receiving sertraline showed steeper reductions in depressive symptoms than placebo participants if their environments were rated as more positive, or less negative. Similarly, participants receiving sertraline compared with placebo were more likely to be abstinent from heroin and cocaine by 12 weeks if their environment was less negative than if it was more negative, but a positive environment did not moderate the effects of sertraline on heroin and cocaine use.

In a pilot noncomparative study, McDowell et al. (2000) examined the efficacy of 150 mg of venlafaxine (serotonin-norepinephrine reuptake inhibitors) for patients ($n=12$) having cocaine dependence and co-occurring depression, as per DSM-III-R criteria. The results indicated significant improvement in Hamilton Rating Scale for Depression, days per week using cocaine, and the average amount of money spent per week on cocaine by week 2, with maintenance of these gains lasting throughout the 12 weeks of the study.

Treatments for Substance-Related Disorders and Comorbid Anxiety Disorders

Substance-Related Disorders and Posttraumatic Stress Disorder. Exposure-based therapies (Foa and Meadows, 1997; Foa et al., 1991) for posttraumatic stress disorder (PTSD) have been extensively studied and have been suggested as the treatment of choice for managing PTSD (Ballenger et al., 2000). For both combat and noncombat-related PTSD, exposure therapy has been shown to reduce significantly both PTSD symptoms and symptoms related to the disorder (e.g., depression; Foa et al., 1999; Hembree and Foa, 2000).

Although exposure-based therapies are considered a first-line treatment for PTSD, psychotherapy experts

Table 2. Outcomes of Treatments for Individuals with Any Substance-Related Disorder and Comorbid Depressive Disorder

Source	Interventions	Group <i>n</i>	Randomized Design	Initial Abstinence	Substance- Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Substance- Related Outcomes Effect Sizes (Cohen's <i>d</i>)
<i>Psychosocial Interventions</i>									
Charney et al. (2001)	(T) Integrated intervention	43			DSM-IV Substance-related disorder	DSM-IV Depressive disorder	6 Months	48% decrease in BDI scores	31.5% decrease in drug use
	(C) No control	0	No	No				42% decrease in HAM-D scores	
<i>TCA's</i> Nunes et al. (1998)	(T) Imipramine 300 mg/d + methadone	74	Yes	No	Patient at methadone Clinic	DSM-III-R Depressive disorder	12 weeks	(1) HAM-D*	(1) Days per week, any substance use*
	(C) Placebo + methadone	63							
<i>SSRIs</i> Petrakis et al. (1998)	(T) Fluoxetine 60 mg/d + methadone	23	Yes	No	Patient receiving methadone maintenance	DSM-III-R MDD Dysthymia Depression NOS	12 weeks	(1) HDRS (2) BDI	(1) Days of cocaine use (2) Days of heroin use
	(C) Placebo + methadone	21							(3) ASI composite (1) % positive urine for cocaine
Schmitz et al. (2001)	(T) Fluoxetine 40 mg/d + CBT	34	Yes	Yes	DSM-IV cocaine dependence	DSM-IV MDD	12 weeks	(1) HAM-D (2) BDI	NC NC
	(C) CBT + placebo	34							
Carpenter et al. (2004)	(T) Sertraline 200 mg/d + methadone	47	Yes	No	patient at methadone clinic	DSM-III-R MDD or DD	12 weeks	(1) HAM-D	(1) % days of cocaine/heroin use (2) % days any drug use
	(C) methadone	48							
<i>Serotonin-norepinephrine reuptake inhibitors</i> McDowell et al. (2000)	(T) Venlafaxine	12	No	No	DSM-III-R Cocaine Dependence	DSM-III-R MDD	12 weeks	Significant reduction in HAM-D scores	Significant reduction in days per week cocaine use
	(C) No control condition	0							

T, Treatment Condition; C, Comparison Condition; MDD, Major Depressive Disorder; DD, Dysthymic Disorder; NC, not calculable; HAM-D, Hamilton Depression scale; HAM-A, Hamilton Anxiety scale; BDI, Beck Depressive Inventory.

*Significant difference ($p < .05$).

Initial Abstinence = Yes if patients were abstinent before beginning treatment.

Cohen's *d* represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

recommend that they be considered a “second-line” treatment for patients having comorbid SUDs (Foa et al., 1999) until the substance use problems are managed. Very few studies have examined the efficacy of exposure or nonexposure-based therapies in individuals with PTSD and comorbid SUD, and fewer still have conducted randomized trials. Given the limited number of studies, it is difficult to determine their efficacy for this subgroup of dually diagnosed individuals, although early evidence indicates that CBT and Relapse Prevention may help reduce both PTSD symptoms and substance use.

We found only one study examining exposure-based therapy for dually diagnosed individuals. While the results appear promising, the study did not include a comparison condition. Brady et al. (2001) provided imaginary and in vivo exposure therapy combined with cognitive-behavioral relapse prevention techniques to 39 cocaine-dependent participants with PTSD (see Table 3). A total of 15 participants completed treatment, and change from pretreatment to posttreatment in these patients indicated significant reductions in intrusive, avoidant, and hyperarousal symptoms, depressive symptoms, and drug-use severity.

“Seeking Safety,” an integrated CBT addressing trauma-related issues in the context of substance use, was developed for the treatment of women with noncombat-related PTSD and substance dependence (Najavits et al., 1998). The study provided 24 structured therapy sessions, integrating cognitive, behavioral, and interpersonal coping skills to 27 women with PTSD and any substance dependence, without a comparison group. Substance use reduced significantly at both posttreatment and 3-month follow-up, and both trauma-related and depressive symptoms improved significantly at 3-month follow-up. Hien et al. (2004) conducted a study comparing “Seeking Safety” treatment with a relapse prevention group and a community care group for women with a SUD and PTSD. Seventy-five women were randomly assigned to either Seeking Safety or relapse prevention group oriented to SUD treatment, and were compared with 32 women in a community care group. At the end of 3 months of treatment, both the Seeking Safety and relapse prevention groups were significantly better than community care at reducing PTSD severity and substance abuse severity, with effect sizes ranging from 0.59 to 0.94. These results were maintained at 6 months after baseline assessment. At 9-month postbaseline, both of the active interventions maintained improvement in PTSD symptoms compared with the community care group. Participants in the relapse prevention condition demonstrated sustained improvement at 9 months for substance use severity, whereas Seeking Safety participants did not significantly differ from the community care group on substance use outcomes. The authors suggested that relapse prevention skills might have generalized to PTSD-related problems, such as attending to emotional triggers, self-care, or safety.

In a medication trial, Labbate et al. (2004) compared sertraline (150 mg) with placebo in 92 individuals with comorbid PTSD and alcohol-related disorder for 12 weeks, and all participants received 1 h/wk of CBT. No significant differences were observed at 12 weeks between the 2 groups in improvements on percent days drinking, total drinks per day, drinks per drinking day, CAPS scores, and HAM-D scores. These results indicate that sertraline does not provide added benefit to CBT in reducing PTSD symptoms, depressive symptoms, or drinking behavior.

Substance-Related Disorder and Social Anxiety Disorder. One psychosocial and one medication study have examined treatment efficacy for social anxiety disorder and comorbid alcohol-related disorder. In a randomized trial, Randall et al. (2001b) tested whether integrated treatment of social anxiety disorder and alcohol dependence, compared with treatment of alcohol dependence alone, further improved alcohol outcomes. The study compared a manualized CBT that treated both social anxiety disorder and alcohol dependence ($n = 49$) with a CBT treatment for alcohol dependence alone ($n = 44$). Both groups showed significant reductions from pre- to postintervention in social anxiety symptoms and alcohol use. However, no group differences were observed in social anxiety outcomes. Furthermore, contrary to the authors’ hypothesis, the group also treated for anxiety problems had worse outcomes on some alcohol-related measures. The authors speculated that the exposure to social or feared situations in dual treatment might have led to drinking to cope in some patients.

In a small study, Randall et al. (2001a) examined the efficacy of paroxetine (SSRI) for the treatment of social anxiety disorder and alcohol abuse or dependence. Participants were randomized to either 60 mg/d of paroxetine ($n = 6$) or placebo ($n = 9$), with treatment lasting 8 weeks. Using the Liebowitz Social Anxiety Scale, participants receiving paroxetine showed significantly greater reductions in both the fear/anxiety and avoidance subscales. While no differences were observed on the Social Phobia Index, the effect size was 0.81. No significant alcohol-related outcomes were observed between those receiving paroxetine and those receiving placebo, although moderate effect sizes favoring paroxetine were observed (between .62 and .81).

Substance-Related Disorders and Panic Disorder. Bowen et al. (2000) examined the efficacy of CBT oriented toward panic disorder in addition to the regular inpatient alcoholism treatment program among alcoholic patients with panic disorder (with and without agoraphobia). Comparing the CBT+alcohol treatment with the alcohol treatment alone, they found no increased efficacy for the CBT condition on anxiety symptoms or drinking outcomes.

Substance-Related Disorder and Generalized or Non-specific Anxiety Disorders. We found 4 studies, all on

Table 3. Outcomes of Treatments for Individuals with Substance-Related Disorder and Comorbid Anxiety Disorder

Source	Interventions	Group n	Randomized Design	Initial Abstinence	Substance- Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Substance-Related Outcomes Effect Sizes (Cohen's <i>d</i>)
<i>Posttraumatic stress disorder psychosocial interventions</i>									
Hien et al. (2004)	(T) Seeking safety (SS) (C1) Relapse prevention (RP) (C2) Community care (CC)	41 34 32	Yes	No	DSM-IV Substance dependence	DSM-IV Current or subthreshold PTSD	24 sessions	SS versus CC (1) PTSD Severity* RP versus CC (1) PTSD Severity*	SS versus CC (1) Substance use severity* RP versus CC (1) Substance use severity*
Brady et al. (2001)	(T) Exposure therapy+relapse prevention (C) No control condition	15 0	No	No	Cocaine dependence	PTSD	16 sessions	Significant decrease in PTSD symptoms	Significant reduction in ASI drug and alcohol composites
Najavits et al. (1998)	(T) Seeking safety (C) No control condition	27 0	No	No	Any substance dependence	PTSD	24 sessions	Significant reduction in subtle trauma symptoms and depression	Significant reduction in ASI drug use composite
<i>Posttraumatic stress disorder SSRI</i>									
Labbate et al. (2004)	(T) Sertraline+CBT (C) Placebo+CBT	48 44	Yes	Yes	DSM-IV Alcohol abuse or dependence	DSM-IV PTSD	12 weeks	(1) HAM-D	(1) Drinks per drinking day
<i>Social Anxiety Disorder</i>									
Randall et al. (2001a)	(T) CBT for alcohol use and social anxiety disorder (C) CBT for alcohol use only	49 44	Yes	No	DSM-III-R Alcohol Dependence	DSM-III-R Social Phobia	12 sessions	(1) Social phobia and Anxiety scale total (2) Liebowitz Social Anxiety Scale total	(1) % days abstinent* (2) % days heavy drinking* (3) Total Drinks Consumed* (4) Drinks per drinking day
Randall et al. (2001b)	(T) Paroxetine 60 mg/d+motivational interviewing (C) Placebo+motivational interviewing	60 9	Yes	No	DSM-IV Alcohol abuse or dependence	DSM-IV Social anxiety disorder	8 weeks	(1) Social phobia index (2) Clinical global index (improved/not improved)	(1) % days abstinent (2) % days heavy drinking (3) Drinks per Drinking Day (4) Total Drinks
<i>Panic Disorder</i>									

Author et al. (Year)	Treatment (T) (C) Usual	Sample Size (T) (C)	Yes	Interview of recent drinking history	DSM-III-R Panic disorder	6 sessions	(1) Fear of Negative Evaluation Scale (2) Social Anxiety and Distress Scale (3) BDI (4) Marks-Mathews Fear Questionnaire	(1) % Abstinent, past 3 months (2) Total drinks past 3 months
<i>GAD and Non-Specific Anxiety</i>								
Tollefson et al. (1992)	(T) Buspirone 60 mg/d (C) Placebo	42 20	Yes	DSM-III Alcohol Abuse or Alcohol dependence	DSM-III Generalized anxiety disorder	24 weeks	(1) HAM-A* (2) HAM-D (3) HSCL-90 Anxiety Sub-scale	(1) Patient assessment of drinking improvement* (2) Clinician assessment of patient drinking improvement
Kranzler et al. (1994)	(T) Buspirone 60 mg/d+CBT (C) Placebo+ CBT	60 30	Yes	DSM-III-R Alcohol dependence	DSM-III-R Any anxiety disorder HAM-A > 14	12 weeks	(1) HAM-A	(1) # drinking days (2) Avg drinks per day (3) drinks per drinking day
McRae et al. (2004)	(T) Buspirone 60 mg/d (C) Placebo	19 17	Yes	DSM-IV Opioid dependence	HAM-A > 17	12 weeks	(1) HAM-A (2) BAI (3) HAM-D (4) BDI	(1) Days to first substance use (2) Days to post-tive urine screen
Malcolm et al. (1992)	(T) Buspirone 60 mg/d (C) Placebo	60 34	No	DSM-III-R Alcohol dependence	DSM-III-R Generalized anxiety disorder	26 weeks	(1) Full response (HAM-A < 18 and > 30% reduction in HAM-A scores)	(1) Months to first drink (2) Months to first intoxication (3) Months to 5 consecutive heavy drinking days

T, Treatment Condition; C, Comparison Condition; NC, Not calculable; HAM-D, Hamilton Depression scale; HAM-A, Hamilton Anxiety scale; BDI, Beck Depressive Inventory.
 *Significant difference ($p < .05$).
 Initial Abstinence = Yes if patients were abstinent before beginning treatment.
 Cohen's d represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

buspirone and with a randomized design, showing little support for its efficacy for individuals with nonspecific anxiety and comorbid substance-related disorder. Tollefson et al. (1992) conducted a randomized trial of buspirone in 42 individuals diagnosed with a DSM-III diagnosis of alcohol abuse or dependence and a comorbid generalized anxiety disorder (GAD). Patients were randomized to receive 15 mg/d of buspirone ($n = 22$) or placebo ($n = 20$), and were followed for 24 weeks. Compared with those receiving placebo, participants receiving buspirone showed significant reduction in HAM-A scores by the end of treatment (Cohen's $d = 0.80$). Participants receiving buspirone rated their drinking as significantly reduced compared with those receiving placebo ($d = 0.66$). However, no significant medication effect was observed for physician-rated change in drinking outcomes, although the effect size was 0.52.

Sixty-one participants with a DSM-III-R diagnosis of alcohol dependence and any anxiety disorder were randomly assigned to receive buspirone ($n = 31$) or placebo ($n = 30$) and were followed for 12 weeks (Kranzler et al., 1994). The buspirone group did not show significant improvement in anxiety or drinking outcomes, although there was a trend toward significance for both outcomes, with effect sizes in the medium range (approximately 0.4 for both outcomes).

McRae et al. (2004) examined the efficacy of buspirone for treating anxiety symptoms in individuals who met DSM-IV criteria for opioid dependence and scored 18 or higher on the Hamilton Anxiety Scale (HAM-A). Participants were randomly assigned to receive buspirone ($n = 19$) or placebo ($n = 17$). Outcomes included both anxiety (HAM-A and Beck Anxiety Inventory) and depressive (HAM-D and BDI) symptoms and time to first drug use. The results indicated no significant difference between buspirone and placebo groups in all outcome measures.

Malcolm et al. (1992) compared buspirone (60 mg/d; $n = 33$) with placebo ($n = 34$) with participants meeting DSM-III-R criteria for alcohol dependence and GAD. Alcohol-related outcomes were assessed using the ASI and the Time-Line Follow Back (TLFB); anxiety outcomes were measured using the HAM-A and the State-Trait Anxiety Scale. The results indicated no differences in anxiety or alcohol use response between the buspirone and placebo conditions.

Treatments for Substance-Related Disorder and Comorbid Schizophrenia

Psychosocial Treatments. Some evidence suggested that integrated treatment may be better than "treatment as usual" among patients with comorbid schizophrenia and substance-related disorders. Barrowclough et al. (2001) devised an integrated treatment that combined cognitive-behavioral, family intervention, and motivational interviewing for patients with comorbid schizophrenia

and SUDs (Table 4). Patients were randomized to the integrated treatment ($n = 18$) or a routine care condition ($n = 18$). Patients in the integrated treatment condition showed significantly better improvement in Global Functioning at 1-year follow-up compared with the routine care condition ($d = 1.37$). In addition, those receiving integrated treatment showed significant improvement in positive symptoms ($d = 0.97$), an increase in percent days abstinent from alcohol and drugs (over 12-months; $d = 0.76$), and less symptom exacerbation. Significantly fewer participants in the integrated treatment condition relapsed ($d = 0.71$), although the number of days spent in relapse was not significantly different for the 2 conditions.

Haddock et al. (2003) extended the outcome data described by Barrowclough et al. (2001) to 18 months, again comparing CBT+motivational interviewing (CBT+MI) with routine care (i.e., medication and case management). The primary outcome was change on the Global Assessment of Functioning (GAF) scale from the DSM-IV. Secondary outcomes included the Positive and Negative Syndrome Schedule (PANSS), the Social Functioning Scale (SFS), and patient substance use as measured by the TLFB. The results indicated that at 18 months postbaseline, those assigned to the CBT+MI condition had significantly higher GAF scores and significantly lower negative symptoms. However, there were no significant differences between treatment conditions on substance use outcomes.

Hellerstein et al. (1995) compared an integrated with a nonintegrated treatment for 47 individuals with a Research Diagnostic Criteria (RDC) diagnosis of schizophrenia and concurrent DSM-III-R diagnoses of any substance-related disorder. Participants randomized to the integrated treatment ($n = 24$) received outpatient supportive group therapy and psychoeducation twice per week and psychopharmacological treatment at a single treatment location and with a theoretical orientation integrated from mental health and substance abuse services. Those randomized to the nonintegrated condition ($n = 23$) received equivalent substance abuse and psychiatric treatment, but from separate treatment facilities. The results indicated that both groups significantly improved at both 4- and 8-month postbaseline assessments on substance use and psychiatric outcomes (Addiction Severity Index drug, alcohol, and psychiatric composite scores), but no differences were observed between the 2 conditions (effect sizes ranged from -0.19 to -0.51).

Shaner et al. (2003) conducted a feasibility study of Substance Abuse Management Module, a skills training approach, for 34 participants with DSM-IV diagnoses of schizophrenia and substance dependence, with no comparison group. Many participants were dependent on more than 1 drug, with cocaine, alcohol, and marijuana being the most common. Substance Abuse Management Module combined components of relapse prevention with social and independent living skills training. Sessions were

Table 4. Outcomes of Treatments for Individuals with Substance-Related Disorder and Schizophrenia

Source	Interventions	Group <i>n</i>	Randomized Design	Initial Abstinence	Substance- Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Substance-Related Outcomes Effect Sizes (Cohen's <i>d</i>)
<i>Psychosocial Interventions</i>									
Barrowclough et al. (2001), and Haddock et al. (2003)	(T) CBT + motivational interviewing (C) Routine care	18	Yes	No	DSM-IV Any substance-related disorder	DSM-IV Schizophrenia, Schizoaffective	29 sessions	(1) GAF score* 1.37 (2) PANSS positive symptoms* 0.97 (3) PANSS negative symptoms* 0.40 (4) PANSS Total 0.49 (5) Social functioning scale 0.66	(1) % Relapse* 0.71 (2) % days abstinent, all substances* 0.76
Hellerstein et al. (1995)	(T) Integrated treatment (C) Non-integrated treatment	24	Yes	Yes	DSM-III-R Any substance-related disorder	RDC Schizophrenia-contingent disorder	8 months	(1) ASI psychiatric composite score -0.51	(1) ASI drug composite score -0.19
Shaner et al. (2003)	(T) Skills training (C) No comparison group	34	No	No	DSM-IV Any substance dependence	DSM-IV Schizophrenia		Significant improvement in quality of life	Significant decline in days of drug use
Drake et al. (1993)	(T) Assertive case management (C) No control condition	18	No	No	DSM-III-R Alcohol-related disorder	DSM-III-R Schizophrenia	4 years longitudinal		61.1% of patients were in remission 4-year postbaseline
<i>Medication Treatments</i>									
Petrakis et al. (2004)	(T) Naltrexone 50 mg/d + CBT (C) Placebo + CBT	16	Yes	No	DSM-IV Alcohol-related disorder	DSM-IV Schizophrenia, Schizoaffective	12 weeks	(1) PANSS total 0.70	(1) Mean drinking days* 1.63 (2) Mean heavy drinking days* 1.16 (3) Self-reported craving* 1.32

T, Treatment Condition; C, Comparison Condition; NC, Not calculable; PANSS, Positive and Negative Syndrome Schedule; CBT, cognitive-behavioral therapy; RDC, Research Diagnostic Criteria; ASI, anxiety sensitivity index.

* Significant difference ($p < .05$).
Initial Abstinence = Yes if patients were abstinent before beginning treatment.
Cohen's *d* represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

offered 5 times per week for approximately 15 weeks. Participants significantly reduced their drug use and showed an improvement in both psychiatric symptoms and quality of life.

Drake et al. (1993) piloted an integrated treatment on 18 participants meeting DSM-III-R criteria for schizophrenia and alcohol-related disorder, with no comparison group. Participants were continuously evaluated for 4 years while being provided assertive case management (i.e., at least weekly visits with a case manager), antipsychotic medications, housing supports, and behaviorally oriented individual substance abuse counseling. Of the 18 participants, 11 showed no evidence of alcohol abuse for at least 6 months, with a mean length of remission of 26.5 months. No data were collected on psychiatric symptoms.

Medication Treatments. We found only one study examining the efficacy of medication for individuals diagnosed with schizophrenia and substance-related disorder. Petrakis et al. (2004) conducted a double-blind randomized clinical trial on the efficacy of naltrexone on 31 patients with a DSM-IV diagnosis of either schizophrenia or schizoaffective disorder and co-occurring alcohol abuse or dependence. Over the course of 12 weeks, patients received a daily dose of 50 mg naltrexone or placebo as well as their routine neuroleptic medication and weekly CBT focusing on relapse prevention and social skills training. Primary outcomes included the frequency and quantity of alcohol use, alcohol craving, and both positive and negative symptoms of schizophrenia. The results indicated that those receiving naltrexone reported significantly fewer heavy drinking days ($d = 1.63$), drinking days ($d = 1.16$), and alcohol cravings compared with those in the placebo condition ($d = 1.32$). There were no significant differences between the 2 conditions in either positive or negative psychotic symptoms, although the mean effect size was 0.70.

Studies Examining Substance-Related Disorders and Comorbid Bipolar Disorder

Psychosocial Treatments. There is weak evidence showing that integrated treatment may be more efficacious than treatment as usual for patients with substance-related disorders and comorbid bipolar disorder. Schmitz et al. (2002) examined the efficacy of an integrated CBT for patients with a DSM-IV diagnosis of bipolar disorder and any SUD (Table 5). Participants ($N = 46$) were randomly assigned to either a medication management (MM; $n = 21$) or MM+CBT ($n = 25$). Medication management consisted of four 20-minute sessions to discuss medication compliance, side effects, drug use, and mood symptoms. In addition to the MM sessions, MM+CBT included 16 individual therapy sessions lasting 60 minutes each and covering relapse prevention, cognitive-behavioral model of substance abuse, depression management model, and cognitive therapy for bipolar disorder. All participants

received maintenance therapy for their bipolar symptoms with divalproex sodium or lithium carbonate. Outcomes included self-reported days of drug and alcohol use since the previous assessment (occurring every 2 weeks for 12 weeks), SADS-C, and the BDI. Participants in the MM+CBT condition were more likely to attend clinic visits, take their medication as prescribed, and report fewer days of experiencing manic symptoms ($d = 2.53$). However, no differences were observed in substance use or days reporting depressive symptoms by the end of treatment, although effect sizes ranged from -0.11 to 1.79.

In a pilot study, Weiss et al. (2000) compared the efficacy of a manual-based integrated group therapy (IGT; $n = 21$) with a no-treatment condition ($n = 24$). Participants met DSM-IV criteria for bipolar disorder and any substance-dependence diagnosis. The most common primary substances of abuse were cocaine, cannabis, and sedative-hypnotic drugs. Participants assigned to the IGT condition received either 12 or 20 group sessions lasting 1 hour each. These sessions focused on denial, ambivalence, acceptance, self-help groups, and identifying and fighting triggers. Participants receiving IGT had significantly greater reductions in drug use as measured by the ASI drug and alcohol composite scores (mean effect size = 0.70). Trends toward significance with moderate effect sizes were also observed for days of drug use and days of alcohol use. For psychiatric outcomes, those in the IGT condition demonstrated significant improvement in the Young Mania Rating Scale (YMRS) compared with control participants ($d = 0.63$), but no differences were observed for HAM-D scores.

Medication Treatments. Salloum et al. (2005) studied the efficacy of valproate for individuals with comorbid DSM-IV bipolar I disorder and alcohol dependence. Using a double-blind, placebo-controlled design, 59 participants were randomized to receive lithium+valproate ($n = 29$) or lithium+placebo ($n = 30$) for 24 weeks. Compared with participants receiving placebo, those receiving valproate showed a significant reduction in percent days drinking heavily, number of drinks per heavy drinking day, and number of drinks per drinking day (mean effect size = 0.89). However, no differences were observed in psychiatric outcomes, including the Beck-Rafaelsen Mania Scale and the HAM-D scale.

Geller et al. (1998) examined the efficacy of lithium in 25 adolescents with primary bipolar disorder and comorbid substance dependence. Participants were randomized to receive lithium (maximum dose = 2,400 mg) or placebo for 6 weeks. Compared with patients receiving placebo, those receiving lithium showed significant improvement in substance use (as measured by a urine test) and global functioning, as measured by the Children's Global Assessment Scale.

Nunes et al. (1990) conducted an open trial of lithium for individuals seeking treatment for cocaine dependence who also had a comorbid DSM-III-R primary diagnosis of

Table 5. Outcomes of Treatments for Individuals with Substance-Related Disorder and Bipolar Disorder

Source	Interventions	Group Randomized Design	Initial Abstinence	Substance-Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Substance-Related Outcomes Effect Sizes (Cohen's <i>d</i>)
<i>Psychosocial Interventions</i>								
Schmitz et al. (2002)	(T) CBT + medication monitoring (C) Medication monitoring	Yes	No	DSM-IV Any substance-related disorder	DSM-IV Bipolar disorder	16 sessions	(1) Days reporting depressive symptoms (2) Days reporting manic symptoms*	(1) Days of drug use (2) Days of alcohol use
Weiss et al. (2000)	(T) Integrated group therapy (C) No-treatment control	No	No	DSM-IV Any substance-dependence	DSM-IV Bipolar disorder	6 months	(1) YMRS* (2) HAM-D	(1) ASI alcohol* (2) ASI drug* (3) Days of alcohol use (4) Days of drug use
<i>Medication Treatments</i>								
Salloum et al. (2005)	(T) Valproate+Lithium+CBT (C) Placebo+Lithium+CBT	Yes	Yes	DSM-IV Alcohol dependence	DSM-IV Bipolar disorder	24 weeks	(1) Mania (2) Depression	(1) Proportion of heavy drinking days* (2) Drinks per heavy drinking day* (3) Proportion of drinks per drinking days (4) Drinks per drinking day* (1) % positive urine sample
Geller et al. (1998)	(T) Lithium (C) Placebo	Yes	No	DSM-III-R Any substance-related disorder	DSM-III-R Bipolar disorder	6 weeks	(1) Global Functioning Score	No significant reduction in cocaine use or craving
Nunes et al. (1990)	(T) Lithium (C) No comparison condition	No	No	DSM-III-R Cocaine abuse or dependence	DSM-III-R Bipolar disorder	12 weeks	No significant reduction in HAM-D scores	Significant reduction in days of alcohol per week, but no significant reduction in drinks per week.
<i>Medication Treatments</i>								
Longoria et al. (2004)	(T) Quetiapine (C) No comparison condition	No	No	DSM-IV Cocaine abuse or dependence	DSM-III-R Bipolar disorder	12 weeks	Significant reduction in HAM-D scores, BPRS scores, and YMRS scores.	Significant reduction in cocaine craving, but no significant reduction in days per week or dollars per week cocaine used.
Brown et al. (2003)	(T) Lamotrigine (C) No comparison condition	No	Yes	DSM-IV Cocaine dependence	DSM-IV Bipolar disorder	12 weeks	Significant reduction in HAM-D scores, BPRS scores, and YMRS scores.	Significant decrease in number of days using drugs
Brady et al. (1995)	(T) Valproate (C) No comparison condition	No	No	DSM-III-R Any substance dependence	DSM-III-R Bipolar Disorder	16 weeks	Significant reduction in HAM-D scores	Significant reduction in alcohol craving, dollars per week spent on alcohol, but not days per week of alcohol use. Significant reduction in cocaine craving, but not dollars per week or days used.
Brown et al. (2005)	(T) Aripiprazole (C) No comparison condition	No	No	DSM-IV Abuse or Dependence on cocaine, amphetamines, cannabis, opiates, or alcohol	DSM-IV Bipolar Disorder, or schizoaffective disorder-bipolar type	12 weeks	Significant reduction in HAM-D scores, YMRS scores, and BPRS scores.	

T, Treatment Condition; C, Comparison Condition; NC, Not calculable; HAM-D, Hamilton Depression scale; HAM-A, Hamilton Anxiety scale; BDI, Beck Depressive Inventory; BPRS, Brief Psychiatric Rating Scale; YMRS, Young Mania Rating Scale.

*Significant difference ($p < .05$).
Initial Abstinence = Yes if patients were abstinent before beginning treatment.
Cohen's *d* represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

bipolar disorder. Ten participants completed between 3 and 12 weeks of treatment and were given between 600 and 1,500 mg/d of lithium. Results indicated no significant reduction in either psychiatric symptoms (Hamilton scale for depression and the hypomania score on the General Behavior Inventory) or cocaine use (self-reported cocaine use, cocaine craving, the Cocaine High scale, and urine tests for cocaine use). In a noncomparative study, Longoria et al. (2004) found that patients ($N = 17$) with bipolar disorder and comorbid cocaine abuse or dependence receiving quetiapine (~ 250 mg/d) had lower HAM-D, YMRS, and Brief Psychiatric Rating Scale (BPRS) outcomes. The primary substance-related outcome was alcohol use, although participants' primary substance disorder was cocaine. Participants significantly reduced their days of alcohol per week, but not drinks per week. Brown et al. (2003) studied 33 participants with DSM-IV cocaine dependence and bipolar disorder. Participants received up to 300mg/d of lamotrigine, with no comparison group, and were followed for 12 weeks. Participants showed significant reduction in HAM-D, YMRS, and BPRS scores, as well as cocaine craving. However, no significant reduction was found in days per week of cocaine use.

Brady et al. (1995) examined the efficacy of valproate (depakote) on participants ($N = 9$) meeting DSM-III-R criteria for bipolar disorder and current substance dependence, with no comparison group. The average maintenance dose of valproate was 1,583 mg/d. Participants were followed for an average of 16 weeks and results indicated significant decreases in depressive (HAM-D scores) and manic (YMRS) symptoms. In addition, participants reported a significant decrease in their quantity of substance use compared with baseline values, with participants using 6% their baseline levels of substances during the first month of treatment. Brown et al. (2005) found that receiving 30mg/d of aripiprazole was significantly associated with a reduction of HAM-D, YMRS, and BPRS scores in 20 participants with bipolar disorder and substance-related disorder. The participants also reported significant reductions in substance craving outcomes, but not days per week of substance use.

Studies Examining Substance-Related Disorders and Severe Mental Illness

While the studies mentioned to this point have focused on specific categories of mental illness, the remaining studies examine treatment efficacy for individuals with any substance-related disorder, and any comorbid nonspecific severe mental illness. There was little evidence showing the advantage of integrated treatment over treatment as usual for patients with substance-related and severe mental illness.

Psychosocial Treatments. Lehman et al. (1993) examined the efficacy of an integrated treatment for patients meeting DSM-III-R criteria for lifetime schizophrenia,

schizoaffective, bipolar or major depressive disorder, and a lifetime substance-related disorder (see Table 6). Components of the program included intensive case management, rehabilitation activities, group therapy, patient and family psychoeducation, and self-help techniques. Participants were randomly assigned to either the integrated program ($n = 29$) or "treatment as usual" (TAU; $n = 25$), which consisted of daytime psychosocial rehabilitation, routine outpatient services, supported housing, and case management. Outcomes included ASI alcohol, drug, and psychiatric composite scores, general life satisfaction, and days in the hospital. Results indicated no improvement in both groups and no advantage for the integrated program over the TAU condition.

Burnam et al. (1995) randomly assigned 276 homeless and dually diagnosed participants to one of 3 conditions: (1) social model residential treatment program, (2) a non-residential program using the same model, and (3) a control condition. Those in the residential program were provided services 24 h/d, 7 d/w, whereas those in the nonresidential program attended services 5 d/wk, between 1:00 and 9:00 PM. Participants in the control condition were free to access available community services (e.g., homeless shelters). Days of alcohol use at 3 months was the only significant difference between treatment and control participants, and the difference disappeared at later assessments.

Drake et al. (1998) conducted a randomized clinical trial comparing an assertive community treatment (ACT; $n = 105$) with standard case management (SCM; $n = 98$), for individuals diagnosed with DSM-III-R co-occurring SUD and severe mental illness, with most participants diagnosed with either schizophrenia or schizoaffective disorder and an alcohol-related disorder. Assertive community treatment utilized several of the same key components of SCM, but the focus of ACT was to provide intensive, integrated, and outreach-oriented services and included: (1) providing services in the community, (2) assertive engagement, (3) continuous 24-hour responsibility, (4) a multidisciplinary, team approach, (5) working closely with support systems, (6) continuity of staffing, (7) high-intensity services, (8) small caseloads, (9) direct substance abuse treatment by members of the team, (10) use of a stage-wise dual-disorders model, (11) dual-disorders treatment groups, and (12) an exclusive team focusing on patients with dual disorders. Participants were followed for 36 months. Participants in both conditions improved significantly on all substance use outcome measures, with those in the ACT condition showing greater improvement on some substance use outcomes, and participants with alcohol use disorders showed greater improvement than those diagnosed with a drug use disorder. When examining general psychiatric outcomes (e.g., stable community days, hospital days, psychiatric symptoms), participants in both treatments improved equally, and those in the ACT condition showed greater improvement than SCM participants in subjective quality of life. In another study, the

Table 6. Non-specific Severe Mental Illness and comorbid substance-related disorder

Source	Interventions	Group n	Randomized Design	Initial Abstinence	Substance-Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's d)	Substance-Related Outcomes Effect Sizes (Cohen's d)
Lehman et al. (1993)	(T) Integrated intervention (C) Treatment as usual	29 25	Yes	No	DSM-III-R Any substance-related disorder	DSM-III-R Schizophrenia, schizoaffective bipolar, or MDD	12 months	(1) ASI psychiatric score (2) Life satisfaction (3) Days in psychiatric hospital	(1) ASI alcohol severity (2) ASI drug severity
Burnam et al. (1995)	(T) Residential treatment program integrated treatment (RT) (C) Community-based non-residential program (NRT)	144 67	Yes	No	DSM-III-R Any substance dependence	DSM-III-R Schizophrenia or major affective disorder	3 months	Combined Treatment versus Control (1) SCL-90-R Depression+Anxiety (2) SCL-90-R Anger+Hostility (3) SCL-90-R Psychoticism	Combined Treatments vs control (1) Days used alcohol* (2) Days used drugs
Drake et al. (1998)	(T) Assertive community treatment (C) Standard case management	105 98	Yes	No	DSM-III-R Any substance-related disorder	DSM-III-R Schizophrenia, Schizoaffective Bipolar Disorder	36 months	(1) BPRS total score (2) QOLI life satisfaction (3) Financial support adequacy* (4) Community Living Skills	(1) SATS score* (2) AUS score* (3) Days alcohol use, past 6 months (4) DUS (5) Days drug use, past 6 months
Jerrell and Ridgely (1995)	(T) Behavioral skills training (BST) (C) Intensive case management (ICM)	39 48	No	No	DSM-III-R Any substance-related disorder	DSM-III-R Psychotic or Major Affective Disorder	18 months	BST versus 12-Step (1) Schizophrenia Sx* (2) Depressive Sx* (3) Mania Sx* (4) Health Status	BST versus 12-step (1) Drug Sx* (2) Alcohol Sx* (3) ICM versus 12-Step (1) Drug Sx (2) Alcohol Sx
Brooks and Penn (2003)	(T) SMART (CBT) intervention (C) 12-step intervention	58 54	No	No	DSM-III-R Any Substance-related disorder	DSM-III-R Schizophrenia, schizo-affective bipolar, MDD	6 months	(1) Social Interaction* (2) ASI Employment* (3) ASI Medical* (4) Health Status	(1) ASI Alcohol Use* (2) Drug Use Scale (3) ICM versus 12-Step (1) Drug Sx (2) Alcohol Sx
Drake et al. (1997)	(T) Integrated treatment (C) Standard community services	158 59	No	No	DSM-III-R Any substance-related disorder	DSM-III-R Schizophrenia, schizo-affective bipolar, MDD	18 months	25 Outcome variables, all non-significant	Dx = Alcohol-related disorder (1) Alcohol Use Scale (2) Drug Use Scale
Sigmon et al. (2000)	(T) Behavior therapy (contingent reinforcement) (C) No comparison condition	18 0	No	No	DSM-IV Marijuana dependence	DSM-IV Schizophrenia, schizoaffective, bipolar, or psychotic disorder	25 weeks	No significant changes in psychiatric symptom severity between baseline and contingency phases.	Negative urine samples for marijuana increased significantly during contingency phase

T, Treatment Condition; C, Comparison Condition; NC, Not calculable.

*Significant difference (p < .05).

Initial Abstinence = Yes if patients were abstinent before beginning treatment.

Cohen's d represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

ACT treatment was shown to be more cost-effective than SCM over time (Clark et al., 1998).

Jerrell and Ridgely (1995) compared the efficacy of 3 treatments for patients ($N = 132$) with a DSM-III-R Axis I diagnosis of either a psychotic or major affective disorder with a co-occurring substance-related disorder. The 3 conditions were a behavioral skills training program, a 12-step recovery program, and an intensive case management program, all oriented to SUD treatment. Participants in the behavioral skills condition were taught self-management, coping, and relapse prevention skills. The 12-step program emphasized fellowship, acceptance of being an addict, working with a sponsor, and education on the disease of alcohol and drug addiction. Case management involved intensive assistance in multiple areas by a clinician or paraprofessional. Compared with the 12-step condition, those in the behavioral skills training program showed a significant improvement in schizophrenia, depressive, mania, drug, and alcohol symptoms based on the Diagnostic Interview Schedule over an 18-month period (effect size range = 0.63–1.26). Those in the case management condition showed a significant improvement in schizophrenia, depressive, and mania symptoms compared with the 12-step approach (effect size range = 0.93–1.05).

Brooks and Penn (2003) compared the efficacy of 12-step and CBT in individuals with a primary DSM-III-R Axis I thought disorder or affective disorder and comorbid substance-related disorder. The cognitive-behavioral intervention, titled “Self-Management and Recovery Training” (SMART), was based upon the principles of Rational Emotive Behavior Therapy. Both conditions placed equal emphasis on mental health and substance use issues. Participants ($N = 112$) were alternately assigned to one of the 2 treatment conditions and met 5 h/d, 5 d/wk for 6 months, but analyses were conducted on only 70 participants who completed 3 months of treatment (final N 's in each group were not reported). The results were mixed. The 12-step condition was significantly better than the SMART condition at reducing alcohol use and increasing social interactions. Conversely, participants in the SMART condition demonstrated superior health ($d = 0.25$) and employment outcomes ($d = 0.31$) than those in the 12-step condition. Both groups showed improvement in alcohol use and life satisfaction.

Drake et al. (1997) compared an integrated mental health, substance abuse counseling, and housing service with a “standard treatment” group for homeless individuals with a severe mental illness diagnosis (i.e., schizophrenia, schizoaffective disorder, bipolar disorder, or major depression) and a substance-related disorder. In contrast to the integrated treatment, participants in the standard treatment condition received services through multiple agencies in the existing housing, substance abuse, self-help, and community mental health systems. When examining substance abuse outcomes, participants with an alcohol-related disorder and in the integrated treatment

condition showed a greater decrease in alcohol use than those in the standard treatment, but participants with drug-related disorders demonstrated similar improvement on drug use outcomes regardless of treatment condition. Days in institutional settings decreased and days in stable housing increased more for those in the integrated treatment than those in the standard treatment. Among the 25 psychiatric and social outcome variables, only 2 demonstrated significantly better outcomes in integrated treatment group: (a) satisfaction with social relations, and (b) amount of social contact. These differences should be viewed with caution, given the number of statistical tests conducted.

Sigmon et al. (2000) examined the effect of contingency management on substance use by providing monetary incentives for negative marijuana urine tests to 18 participants with psychotic disorders and co-occurring marijuana dependence in a noncomparative study. Over the course of 25 weeks, 10 completers were examined on change in the mean number of negative specimens and the mean number of consecutive marijuana-negative specimens. Compared with baseline assessment (i.e., no reward), the mean number of negative specimens and consecutive negative specimens increased when rewards were offered. There was no evidence of drug substitution when marijuana use was reduced by contingent reinforcement, and no evidence that abstinence from marijuana use reduced psychiatric symptoms.

Treatments for Substance-Related Disorder and Comorbid Nonspecific Mental Illnesses

Rahav et al. (1995) compared a therapeutic community (TC) with a community residence (CR) treatment program for 100 homeless men with DSM-III-R diagnoses of: (a) either alcohol (22%) or other drug dependence (78%), and (b) any psychiatric diagnosis (mainly psychotic or mood disorder) and a history of at least 2 psychiatric hospitalizations (Table 7). Therapeutic community was modified to include psychiatric treatment components. Community residence was enhanced to include substance abuse treatment components consisting of substance abuse counselors and training for staff in the treatment of homeless, chemically abusing mentally ill individuals. Overall, 317 participants were randomly assigned to TC and 299 to CR. However, results are based on only 100 participants (48 in TC and 52 in CR) who completed treatment. No substance-related outcomes were included. The results indicated that those assigned to TC showed a significant improvement in both depressive symptoms (CES-D; $d = 0.63$) and GAF scores ($d = 0.77$) through 1 year compared with those in the CR. No significant differences were observed in the Psychotic Ideation scale, Rosenberg Self-Esteem Scale, and the Brief Psychiatric Rating Scale, although effect sizes ranged from 0.29 to 0.43.

Table 7. Other mental illnesses and substance-related disorder

Source	Interventions	Group <i>n</i>	Randomized Design	Initial Abstinence	Substance- Related Criteria	Psychiatric Criteria	Length of Experimental Condition(s)	Psychiatric Outcomes Effect Sizes (Cohen's <i>d</i>)	Substance-Related Outcomes Effect Sizes (Cohen's <i>d</i>)
Rahav et al. (1995)	(T) Therapeutic community residence (C) Community residence	48 52	Yes	No	DSM-III-R Any substance-related disorder	DSM-III-R Any psychiatric disorder	12 months	(1) CES-D* (2) Psychotic Ideation (3) BPRS score (4) GAF* (5) Self-Esteem N/A	0.63 0.43 0.38 0.77 0.29 0.57 N/A
Hulse and Tait (2002)	(T) Motivational interview package (C) Information package	62 58	Yes	Yes	AUDIT > 7	DSM-IV Any psychiatric disorder	6 months	N/A	(1) Change in alcohol use
Milby et al. (2000)	(T) Behavioral day treatment+abstinent contingent housing and work therapy (C) Behavioral day treatment	56 54	Yes	No	DSM-III-R Cocaine Abuse or Dependence	T-score > 70 on HSC-90-R	8 weeks	(1) % days housed (2) % days employed	- 0.29 - 0.56 (1) % abstinent* 0.86
Herman et al. (2000)	(T) Integrated intervention (C) Standard hospital intervention	284 145	Yes	No	DSM-III-R Any substance-related disorder	DSM-III-R Schizophrenia, organic mood, mild affective, adjustment, MDD, Bipolar, Antisocial PDD	4 weeks	N/A	(1) Mean days alcohol use*
Meisler et al. (1997)	(T) Assertive community treatment (C) No comparison condition	67 0	No	No	DSM-III-R Any substance-related disorder	DSM-III-R schizoaffective disorder, bipolar disorder, major depression, paranoid personality disorder, or borderline personality disorder	N/A	N/A	24% of participants were abstinent during year 4, 17% were "mild" substance users
Moggi et al. (1999)	(T) Integrated treatment (C) No comparison condition	52 0	No	No	ICD-10 Any substance-related disorder	ICD-10 Any psychiatric disorder	1 year follow-up	Significant improvement in positive symptoms. No significant improvement in anxiety/depression	No significant reduction in drug use

T, Treatment Condition; C, Comparison Condition; NC, Not calculable.

*Significant difference ($p < .05$).

Initial Abstinence = Yes if patients were abstinent before beginning treatment.

Cohen's *d* represents effect of treatment condition (T) relative to control condition (C), with small, medium, and large effects defined as 0.2, 0.5, and 0.8, respectively.

Hulse and Tait (2002) examined 6-month outcomes of a brief alcohol intervention on 120 individuals in Australia with Alcohol Use Disorders Identification Test scores of >7 and who had an ICD-9 psychiatric diagnosis, with the majority having a mood disorder. Participants were randomly assigned to receive either a motivational interview (MI; $n = 62$) or an information package (IP; $n = 58$). Motivational interviewing was a 45-minute individualized session that covered the benefits and drawbacks of alcohol use and individual written feedback. The information package consisted of information on safer alcohol consumption. At 6-month postbaseline, those assigned to the motivational interviewing group reported significantly lower weekly alcohol consumption than those in the information package group. In a later study, Hulse and Tait (2003) examined 5-year outcomes for those receiving the MI or IP treatments compared with a matched group of control participants who met eligibility criteria but were discharged from the hospital before receiving a brief interview. Participants in the MI and IP conditions were merged to form an overall brief intervention condition. The results indicated significantly greater time to first general hospitalization and to first mental health hospitalization, and fewer days of mental health hospitalization over 5 years for those receiving a brief intervention. Days to first alcohol event approached significance in favor of the brief interventions.

Milby et al. (2000) compared a behavioral day treatment (DT) with a behavioral day treatment plus abstinence-based contingent housing and work therapy (DT+) in homeless nonpsychotic patients with a T -score of 70 or above on the Hopkins Symptom Checklist and diagnosed with cocaine abuse or dependence. Both interventions offered education and group therapy emphasizing individual counseling, relapse prevention, assertiveness training, role play, 12 steps, relaxation, and goal development. However, participants in the DT+ condition were rewarded with a program-provided, rent-free, furnished apartment if they were abstinent for 2 consecutive weeks. Positive results on urine tests resulted in immediate eviction from the rent-free or subsidized housing. During the second phase of the intervention (months 3–6), the DT+ group could participate in abstinence-contingent work therapy based on the same contingencies that housing required. The results at 2- and 6-month follow-ups indicated that compared with those in the DT condition, DT+ participants showed significant increases in percent days abstinent (past 60 days) and more days housed at 6 months. In a later report (Milby et al., 2003), 12-month follow-up outcomes on substance use (i.e., self-report ASI), housing, and employment for the DT and DT+ conditions were examined. An additional 31 participants were included in the study, with a total of 43 in the DT-only condition and 57 in the DT+ condition. The results indicated no significant differences between the groups in substance use, days housed, and days employed. In another study by Milby et al. (2005), 196 homeless

individuals with coexisting cocaine dependence and nonpsychotic mental disorder were provided this same manualized cognitive-behavioral intervention in conjunction with one of 3 housing arrangements: (a) abstinence-contingent housing ($n = 63$), (b) nonabstinence-contingent housing ($n = 67$), and (c) no housing ($n = 66$). The results indicated that compared with the no-housing group, those receiving housing (abstinence or nonabstinence) had a significantly greater abstinence rate across the first 6 months of the study. The prevalence of psychiatric disorders reduced from baseline to 6 months, but was not significantly different between treatment and control groups (Kertesz et al., 2006).

In a randomized clinical trial, Herman et al. (2000) compared an integrated “Mental Health Chemical Dependence” program with a standard short-term treatment ward for mentally ill substance-abusing patients (length of treatment = 51 and 31 days, respectively, on average). All participants had a DSM-III-R diagnosis of substance abuse or dependence and a comorbid mental illness, including schizophrenia, major depressive disorder, adjustment disorder, or antisocial personality disorder. The standard treatment provided stabilization of acute psychiatric and physical symptoms, a half-hour per week of individual therapy, 1 h/wk of group therapy, and relapse prevention. The integrated treatment provided an additional 1 h/wk of individual therapy and 5 h/wk of group therapy that helped participants address drug and alcohol addiction problems, reduce denial, enhance coping skills, and improve interpersonal relationships. The integrated treatment program also offered educational lectures, AA/NA groups, family education sessions, and gender-specific support groups. Compared with those receiving standard treatment, those in the integrated treatment condition demonstrated a 54% reduction in days of alcohol use on the Addiction Severity Index at 2-month postdischarge ($d = 0.41$), but not at other assessments.

Meisler et al. (1997) examined the impact of ACT, with no comparison group, on homeless individuals ($N = 67$) with DSM-III-R diagnosis of SUD and comorbid schizophrenia, schizoaffective, bipolar, major depressive, paranoid personality, or borderline personality disorder, and followed them for 4 years. Assertive community treatment consisted of medication management, facilitating acquisition of basic resources, basic living skills, and support, focusing on both SUD and mental illnesses. The results indicated significant reductions in homelessness and psychiatric hospital use, but no improvement in substance use.

Moggi et al. (1999) examined the efficacy of an integrated inpatient treatment program, with no comparison group, for individuals ($n = 52$) with substance use and schizophrenia, bipolar, depression, and personality disorders. The 4-month intervention consisted of milieu therapy, medication, education about dual diagnosis, relapse prevention, and individual psychotherapy. Despite a decline in the

frequency of use, the results indicated that a pre–post treatment difference was not significant at the 1-year follow-up. Patients showed mixed results on psychiatric outcomes, with significantly fewer positive psychotic symptoms and suspiciousness/hostility, and no improvement in negative psychotic symptoms and anxiety/depression.

CONCLUSIONS

Fifty-nine studies of treatment for individuals with dual diagnosis were found, of which 36 studies were RCTs. Among the RCTs, 13 studies focused on the efficacy of psychosocial treatments and 23 studies examined the efficacy of medication or medication plus psychosocial treatments. This review did not find treatments that had been replicated and consistently showed clear advantages over comparison conditions for both substance-related and other psychiatric outcomes. However, this review found that: (1) existing efficacious treatments for reducing psychiatric symptoms (e.g., TCA for depressive symptoms) also tend to work in dual-diagnosis patients, (2) existing efficacious treatments for reducing substance use (e.g., relapse prevention) also decrease substance use in dually diagnosed patients, and (3) the efficacy of integrated treatment is still unclear, with only weak evidence currently suggesting that integrated treatment are better than “treatment as usual,” partly due to the lack of data and the considerable heterogeneity of team-dependent integrated treatment. Although replication of treatment efficacy is necessary, the following treatments appear promising for either substance-related and/or other psychiatric outcomes and warrant future investigation. Tricyclic assessments may be efficacious in reducing depressive symptoms among depressive substance–abusing individuals. Evidence shows that Seeking Safety and relapse prevention may reduce PTSD and substance-related problems among women diagnosed with PTSD and substance-related disorders. Cognitive–behavioral therapy+motivational interviewing may benefit individuals with substance-related disorder and schizophrenia; naltrexone may reduce alcohol use among individuals with schizophrenia and alcohol-related disorders, and valproate+lithium may reduce alcohol use among individuals with comorbid bipolar and alcohol-related disorders. Enhanced efficacy with a higher dosage of medication is not evident in this review.

The current state of the literature on treatment for individuals with dual diagnosis has many shortcomings. First, more studies are necessary, given the diverse categories of “dual diagnosis.” There are limited numbers of studies that used the same type of intervention (e.g., CBT, SSRI) for patients with the same type of comorbidity (e.g., comorbid depression and alcohol dependence), with the exception that there were 4 studies of sertraline with patients with comorbid depression and alcohol-related disorders. Therefore, determining the efficacy of many treatments is premature. The dearth of studies may be due to the diver-

sity of conditions under the umbrella of “dual diagnosis.” For example, this review classifies studies into broad comorbid diagnostic categories, within which many subcategories were further divided. Not only have few treatments been replicated but also few interventions have shown meaningful improvement in both substance and psychiatric outcomes, regardless of the kind of comorbid diagnoses.

Another problem consists of the weakness of the study designs. Unfortunately, there is a lack of well-controlled, randomized trials, and many studies did not measure either substance use or other psychiatric outcomes. Furthermore, future studies need to consistently make the distinction between primary versus secondary psychiatric disorders or symptoms, and test whether reduction of psychiatric symptoms is mediated or moderated by substance use, and vice versa, to enhance the clarity of the implications of the findings. Coupled with the diversity of outcome measures, small sample sizes, and failure to report information useful for calculating effect sizes, determining the overall efficacy of the interventions is difficult, if not impossible.

Completion rate is low (high attrition) in many studies, and it is not uncommon for researchers to exclude the dropped-out patients from analyses or conduct intent-to-treat analyses using the last observation carried forward technique. These practices can bias results. Therefore, researchers should structure the studies in ways that would better retain participants, or conduct intent-to-treat comparisons using newer methods of imputing missing outcome data, including multiple imputation methods (e.g., Schafer and Graham, 2002).

Many studies failed to examine the effect of total amount of services received on treatment outcomes. Studies that found significant treatment effects often did not consider the fact that those randomized to the active treatment received considerably more therapy time than those in the control condition. Indeed, the total amount of services received may contribute to better outcomes, as was the case for Drake et al. (1997), who found that when participants in the active and comparison conditions received similar amounts of total services, dramatic improvements were seen in both conditions.

The interaction between medication and substance use has not been examined systematically. Future studies should investigate its effects on treatment efficacy because psychiatric medications may have less efficacy or more side effects among persons using psychoactive substances. For example, postsynaptic dopamine receptors of chronic cocaine users, even when detoxified, were found to be depleted; thus, cocaine use may reduce the efficacy of neuroleptics (Volkow et al., 1990).

Attention to racial/ethnic and cultural influences on the outcomes of dual-diagnosis treatment studies was completely lacking. Although limited, there were studies that attended to the cultural influences on SUD or on psychiatric outcomes, but not both. For example, people from

different ethnic groups have been found to require different dosages of psychotropic medications to achieve a therapeutic effect (e.g., Lin et al., 1995). Some evidence shows that cultural sensitivity and competence may be critical to engaging individuals with minority ethnic backgrounds in mental health services (Mercer-McFadden et al., 1997). More knowledge is needed about how cultural factors influence the course of treatment and outcomes for individuals with dual diagnosis.

Besides efficacy studies, effectiveness studies examining factors that are associated with better patient outcomes in the real-world contexts are also crucial in the understanding of treatment of dual-diagnosis patients. Likewise, examining moderating and mediating factors that indicate which types of patients benefit from which specific dual-diagnosis treatments and how treatment, clinician, and treatment environment factors exert their effects will also move the field forward to more effective and cost-effective treatments for dual-diagnosis patients.

The reviewed studies have laid a foundation for future studies. However, the current status of the literature, unfortunately, is so poor that urgent attention by researchers and funding agencies is needed to conduct more and more methodologically rigorous research in this area, given the high prevalence of dual-diagnosis patients. Funding agencies should make funding for studies in this area a high priority, and focus on funding high-quality studies. Studies with rigorous, experimental designs focusing on the various patient categories under the board umbrella of dual diagnosis are necessary. Future studies need to include sufficient sample sizes, maintain high study completion rates, include multiple and long-term outcome measures and measures of moderating and mediating mechanisms, report treatment effect sizes, include patients who dropped out in the analyses, differentiate between treatment effects and the effects of total amount of services patients received, examine cultural influences on treatment processes and outcomes, investigate clinician and program factors that are related to patient outcomes, and evaluate treatment guidelines. Despite a number of promising treatments, there is still a long way before we know what treatments work for which groups of dual-diagnosis patients.

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