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REVIEW ARTICLE

The Canadian Network for Mood and Anxiety Treatments (CANMAT) task force recommendations for the management of patients with mood disorders and comorbid substance use disorders

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BACKGROUND: Mood disorders, especially bipolar disorder (BD), frequently are associated with substance use disorders (SUDs). There are well-designed trials for the treatment of SUDs in the absence of a comorbid condition. However, one cannot generalize these study results to individuals with comorbid mood disorders, because therapeutic efficacy and/or safety and tolerability profiles may differ with the presence of the comorbid disorder. Therefore, a review of the available evidence is needed to provide guidance to clinicians facing the challenges of treating patients with comorbid mood disorders and SUDs.

METHODS: We reviewed the literature published between January 1966 and November 2010 by using the following search strategies on PubMed. Search terms were *bipolar disorder* or *depressive disorder, major* (to exclude depression, postpartum; dysthymic disorder; cyclothymic disorder; and seasonal affective disorder) cross-referenced with *alcohol or drug or substance* and *abuse or dependence or disorder*. When possible, a level of evidence was determined for each treatment using the framework of previous Canadian Network for Mood and Anxiety Treatments recommendations. The lack of evidence-based literature limited the authors' ability to generate treatment recommendations that were strictly evidence based, and as such, recommendations were often based on the authors' opinion.

RESULTS: Even though a large number of treatments were investigated for alcohol use disorder (AUD), none have been sufficiently studied to justify the attribution of level 1 evidence in comorbid AUD with major depressive disorder (MDD) or BD. The available data allows us to generate first-choice recommendations for AUD comorbid with MDD and only third-choice recommendations for cocaine, heroin, and opiate SUD comorbid with MDD. No recommendations were possible for cannabis, amphet-

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amines, methamphetamines, or polysubstance SUD comorbid with MDD. First-choice recommendations were possible for alcohol, cannabis, and cocaine SUD comorbid with BD and only second-choice recommendations for heroin, amphetamine, methamphetamine, and polysubstance SUD comorbid with BD. No recommendations were possible for opiate SUD comorbid with BD. Finally, psychotherapies certainly are considered an essential component of the overall treatment of SUDs comorbid with mood disorders. However, further well-designed studies are needed in order to properly assess their potential role in specific SUDs comorbid with a mood disorder.

CONCLUSIONS: Although certain treatments show promise in the management of mood disorders comorbid with SUDs, additional well-designed studies are needed to properly assess their potential role in specific SUDs comorbid with a mood disorder.

KEYWORDS: bipolar disorder, major depressive disorder, substance use disorders, dual diagnosis, comorbidity, psychopharmacologic treatments, psychosocial treatments

INTRODUCTION

Mood disorders, especially bipolar disorder (BD), frequently are associated with substance use disorders (SUDs).[1] When treating these comorbidities, the clinician faces numerous challenges, such as selecting a treatment that will be efficacious without significantly increasing the risk of destabilizing the mood disorder. Efforts to limit polypharmacy by selecting a medication that will be useful for treating both the mood disorder and SUD is another challenge. Moreover, because the literature on treating these comorbid disorders is relatively scant, it is challenging for clinicians to select the best evidence-based treatment for any given patient. Unfortunately, even though there are rigorous randomized controlled trials (RCTs) for the treatment of SUDs, one cannot assume that these treatments would be efficacious and, most importantly, safe and well tolerated, when applied to patients suffering from a simultaneous mood disorder. The aim herein is to summarize the available evidence pertaining to the treatment of SUDs in individuals with mood disorders to inform treatment decisions in these commonly encountered patients.

Importance of the problem

Numerous epidemiological and clinical studies[2-8] have demonstrated that SUDs are highly prevalent among patients suffering from a mood disorder. In a recent Canadian epidemiological study where sociodemographic variables, clinical variables, and depressive symptomatology were compared between patients with BD (n = 467) and major depressive disorder (MDD; n = 4,145), the authors found an average past-year problematic SUD of 29% (23.1% to 34.8%) for BD and 14.3% (12.8% to 15.8%) for MDD.[9] The odds ratio (OR) for developing a SUD is 1.8 in patients with a lifetime MDD and 6.9 for those with a lifetime bipolar I disorder (BD I), compared with the general population.[10] Early-onset BD seems to be even more strongly associated with the development of a comorbid SUD.[11] In addition, SUDs also are considered a risk factor for the development of BD I. In that regard, cocaine use disorder predicts subsequent onset of BD I (OR = 4.2), as does stimulant abuse (OR = 3.1) and dependence (OR = 5.7).[12] In addition, a subgroup of BD patients developed a milder form of affective disorder expressed only after extended exposure to alcohol use disorders (AUD),[13] whereas onset of BD after cannabis use was less pronounced.[14]

Finally, the importance of addressing comorbid SUDs and mood disorders becomes even more evident when one considers that mood disorders often are masked by comorbid SUDs, contributing to diagnostic delay.[15]

METHODS

We have reviewed the available literature published between January 1966 and November 2010 by using the following search strategies on PubMed. Search terms were *bipolar disorder* or *depressive disorder, major* (to exclude depression, postpartum; dysthymic disorder; cyclothymic disorder; and seasonal affective disorder) cross-referenced with *alcohol or drug or substance* and *abuse or dependence or disorder*. Articles were selected on the basis of containing data regarding both BD or MDD and SUDs. The search was supplemented by manually reviewing reference lists from the identified publications. The Cochrane database also was reviewed as well as the Web site clinicaltrials.gov in order to determine the status of unpublished or ongoing studies.

A level of evidence was attributed for each treatment, using the framework of previous Canadian Network for

TABLE 1
Criteria for level of evidence[a] and line of treatment for pharmacotherapies[b]

Evidence level	**Criteria**
Level 1	Meta-analysis or replicated double-blind RCT that includes a placebo condition
Level 2	At least 1 double-blind RCT with placebo or active comparison condition
Level 3	Prospective uncontrolled trial with ≥10 patients
Level 4	Anecdotal reports or expert opinion
Line of treatment	**Criteria**
First choice	Level 1 or Level 2 evidence, plus clinical support[c]
Second choice	Level 3 evidence or higher, plus clinical support[c]
Third choice	Level 4 evidence or higher, plus clinical support[c]

[a]Note that level 1 and 2 evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, therefore the highest level of evidence is usually level 3. Higher-order recommendations (eg, principles of care) reflect higher level judgment of the strength of evidence from various data sources, and therefore are primarily level 4 evidence.
[b]A first-choice treatment represents a balance of efficacy, tolerability, and clinical support. Second-choice and third-choice treatments are reserved for situations where first-choice treatments are not indicated or cannot be used, or when first-choice treatments have not worked.
[c]Clinical support refers to application of expert opinion to ensure that evidence-supported interventions are realistic in clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side-effect or safety profile.

RCT: randomized controlled trial.

Mood and Anxiety Treatments (CANMAT) recommendations.[16] This framework is presented in **TABLE 1**. Treatment recommendations were then generated based on the level of evidence and clinical support available.

As an overarching principle, we collapsed the categories of substance abuse or dependence under the term SUD. This approach is consistent with what has been documented in a large number of studies and with anticipated changes in the upcoming DSM-5. Given the differences in approaches to treatment and the largely independent line of research, the current paper abstains from including recommendations for the management of tobacco use disorder. A large body of literature focuses on therapies for SUDs independent of comorbid mood disorders. Moreover, most of the studies focus on a given SUD comorbid with non-specific mental disorders, often mixing schizophrenia with mood disorders and presenting the results for the whole sample. This makes it difficult to derive conclusions about the efficacy of treatment for a specific mood disorder such as MDD or BD. Moreover, we could not find studies which made a distinction between BD I and bipolar II disorder (BD II).

Many of the pharmacological treatments were studied as an add-on to an often unspecified treatment regimen. Treatment studies also were of various durations, more often acute rather than long term. Some newer medications are not included in our review because of the lack of published evidence for comorbid conditions (eg, acamprosate, buprenorphine and naloxone combination). In addition, we focused only on the psychiatric outpatient population and did not include studies on special populations such as inmates and homeless outpatients. Finally, clinical experience indicates that individuals with SUDs often abuse multiple agents. This is reflected in a large number of the studies where the assessed treatment was for polysubstance use disorder. Therefore, this literature review reports results by therapeutic agent and then makes final treatment recommendations based on the treatment outcome, level of evidence (although frequently extremely limited), and clinical support for each of the SUDs.

RESULTS

The results of our literature review are presented in **TABLE 2**.[17-97] **TABLE 3** summarizes the recommendations we could arrive at for the pharmacologic treatment of mood disorders comorbid with SUDs. The following is a summary of our findings.

Anticonvulsants

Carbamazepine. A 12-week, placebo-controlled RCT of carbamazepine (up to 800 mg/d) was conducted in cocaine-dependent individuals with (n = 57, including 30 MDD patients and 10 BD patients) and without (n = 82) a mood disorder.[17] No other mood stabilizers, antidepressants, or dopamine agonists were allowed. The carbam-

azepine-treated affective group showed a trend toward fewer cocaine-positive urine drug screens (P = .08) and longer time to first cocaine use (P = .06).

Two double-blind, placebo-controlled RCTs of 8-weeks' duration comparing carbamazepine (study 1: n = 5; study 2: n = 47), desipramine (study 1: n = 2; study 2: n = 49), and placebo (study 1: n = 4; study 2: n = 50) in the treatment of cocaine dependence with comorbid MDD found no benefit of either agent compared with placebo.[18,19] Therefore, the available evidence does not support the use of carbamazepine for treating cocaine dependence comorbid with either MDD or BD.

Lamotrigine. No lamotrigine studies were available for SUDs comorbid with MDD. However, adjunctive or monotherapy use of lamotrigine (up to 300 mg/d) was assessed in a 12-week, open-label study for the treatment of AUD comorbid with BD (N = 28).[20] Lamotrigine demonstrated efficacy in decreasing alcohol craving and consumption (P < .001) and improved scores on the 17-item Hamilton Rating Scale for Depression ($HRSD_{17}$), as well as the Young Mania Rating Scale (YMRS) (P < .01). A similar result on mood symptoms was observed in 2 open-label studies of cocaine dependence. An open-label study (N = 30) and a replication study (n = 32) examining lamotrigine as monotherapy (up to 300 mg/d) or as an adjunct to other medications (up to 12.5 mg/d in patients taking valproic acid) in BD, demonstrated efficacy in reducing self-report cravings and cocaine use (both studies: P < .001).[21,22] Based on these initial open-label studies, lamotrigine appears to be a safe and useful treatment for comorbid alcohol or cocaine addiction in BD and a second-choice recommendation is attributed for that treatment.

Topiramate and gabapentin. In a recent review of the literature, 5 out of 8 patients with AUD comorbid with BD improved with topiramate.[23-25] Similarly, in an open-label study of 43 patients refractory to mood stabilizers, patients with comorbid AUD (n = 5) seemed to benefit from gabapentin treatment.[26] Notably, these are preliminary observations, which fulfill only the requirements for a level 4 evidence rating.

Lithium. One large double-blind, placebo-controlled RCT studying the potential role of lithium (mean plasma level: 0.65 mEq/L) as a treatment for AUD in MDD (n = 171) for a duration of up to 1 year, reported negative results.[27] A 6-month, double-blind, placebo-controlled comparison RCT of lithium monotherapy and lithium plus valproic acid was conducted in patients with BD comorbid with alcohol, cannabis, or cocaine abuse or dependence and rapid cycling during the last 12 months (N = 149).[28] Only a small group of patients (n = 31; 21%) met criteria of a minimum of 4 consecutive weeks of stabilization with lithium (blood level ≥.8 mEq/L) plus valproic acid (blood level ≥50 μg/mL) and were then randomly assigned to the double-blind phase of the study. There was a trend toward improvement of substance abuse outcomes. However, given the small sample size, no statistical difference was reported for the 2 treatment groups. An older, very small, open-label study of a heterogeneous group of mood disorder patients (BD: n = 4; MDD: n = 2; and other mood disorder: n = 4) found no benefit with lithium (range: .4 to 1.0 mEq/L) on measures of use and craving for cocaine.[29] Finally, a 6-week placebo-controlled RCT completed in adolescents with BD I and BD II as well as bipolar spectrum (age 16.3 ± 1.2; n = 46) mainly addicted to alcohol (28%), cannabis (8%), or cannabis plus alcohol (56%), reported a decrease on urine drug assays for intent to treat (n = 25; P = .028) as well as for completers (n = 21; P = .042) with mean serum levels of .88 and .79 mEq/L, respectively.[30]

This knowledge certainly is useful given the paucity of data to guide clinicians in treating BD in adolescents and given the frequent comorbid SUDs in this population. However, caution should be used with lithium treatment, especially in alcohol abusers, given that significant interactions leading to lithium intoxication are possible. In addition, there are limited statistically positive outcomes found in the adult population. Therefore, our suggestion is to downgrade this treatment option to a third-choice recommendation for AUD.

Valproic acid. Three add-on open-label studies (N = 41) and 1 retrospective chart review (n = 46 with a diagnosis of BD or mood disorder not otherwise specified [NOS]) were done at various plasma levels of valproic acid (range: 35.3 to 100 mg/mL) in BD patients with alcohol, cocaine, or cannabis use disorder. Some efficacy in decreasing consumption and cravings were shown.[31-34]

One 24-week, placebo-controlled RCT demonstrated efficacy of valproic acid (plasma concentration of 50 to 100 μ/mL) added to lithium in BD (N = 59) presenting with a mood episode plus AUD.[35] The mood symptoms improved equally in both groups, but the valproic acid group (n = 29) had a significantly lower proportion of heavy drinking days (P = .02) and a trend toward fewer drinks per heavy drinking day (P = .055) compared with the placebo group (n = 30). However, randomization to valproic acid treatment or placebo was initiated within

TABLE 2
Level of evidence for pharmacotherapies for treatment of mood disorders comorbid with SUDs

Agent	Substance	MDD	BD
ANTICONVULSANTS			
Carbamazepine	Cocaine	Level 2: negative[17-19]	Level 3: negative[17]
Gabapentin	Alcohol		Add-on: level 4[25,26]
Lamotrigine	Alcohol		Add-on or alone: level 3[20]
	Cocaine		Add-on or alone: level 3[21,22]
Topiramate	Alcohol		Add-on: level 4[23-25]
MOOD STABILIZERS			
Lithium	Alcohol	Level 2: negative[27]	Add-on to valproic acid or alone: level 2[28] [a]level 2[30]
	Cannabis		Add-on to valproic acid or alone: level 2[28] [a]level 2[30]
	Cocaine	Level 4: negative[29]	Add-on to valproic acid or alone: level 2[28,29]
Valproic acid	Alcohol	Level 4[32]	Add-on to lithium: level 2[28,35] Add-on or alone: level 3[31-33]
	Cannabis		Add-on to lithium: level 2[28] Add-on or alone: level 3[31-33]
	Cocaine		Add-on to lithium: level 2[28] Add-on or alone: level 3[31-34]
ANTIDEPRESSANTS			
TCAs			
Amitriptyline	Alcohol	Level 2[36]	
Desipramine	Alcohol	Level 2[37]	
	Cocaine	Level 2: negative[18,19,38,40]	
	Opiate and cocaine	Add-on to opioid maintenance buprenorphine: level 2: negative[39] Add-on to opioid maintenance methadone: level 2: negative[39]	
Imipramine	Alcohol	Level 2[41,42]	
	Cocaine	Level 2: negative[43]	
	Opiate	Add-on to methadone: level 2[44,45]	
SSRIs			
Escitalopram	Alcohol	Level 2[46,47]	
Fluoxetine	Alcohol	Level 2[48-51] [a]Level 2: negative[52-55]	
	Cannabis	[a]Level 2: negative[52,56]	
	Cocaine	Level 3: negative[57,58]	
	Opiate	Add-on to methadone: level 2: negative[50,59]	
Nefazodone	Alcohol	Level 1[60-62]	
	Cocaine	Level 2: negative[63]	
Sertraline	Alcohol	Level 2: negative[50,64-68] Level 2: naltrexone plus sertraline[69]	
	Opiate	Add-on to methadone: level 2: negative[50,70]	

TABLE 2
Level of evidence for pharmacotherapies for treatment of mood disorders comorbid with SUDs (continued)

Agent	Substance	MDD	BD
OTHER			
Mirtazapine	Alcohol	Level 2[36,71]	
ANTIPSYCHOTICS			
Aripiprazole	Polysubstance		Switch from current antipsychotic(s) + Add-on: level 3[72]
Quetiapine	Alcohol		Add-on or alone: level 2/negative[73-76]
	Cocaine		Add-on or alone: level 2[77-79]
	Amphetamines		Add-on or alone: level 2[78]
	Methamphetamines		Add-on or alone: level 2[77]
Risperidone	Cocaine	Add-on or alone: level 4[80]	Add-on or alone: level 2[77,80]
	Methamphetamines		Add-on or alone: level 2[77]
OTHER AGENTS			
Buprenorphine	Heroin	Add-on or alone: level 4[81]	
Citicoline	Cocaine		Add-on: level 2[82]
Disulfiram	Alcohol	Add-on: level 2[83-88]	Add-on: level 2[83,88-90]
Memantine	Alcohol	Level 2[46,47]	
Methadone	Heroin		Level 3[91]
Naltrexone	Alcohol	Add-on or alone: level 2[69,87,88,92,93] Naltrexone plus sertraline: level 2[69] [b]Add-on to sertraline: level 2: negative[94]	Add-on: level 2[87,95-97]

[a]Adolescent cohort.
[b]Age ≥55 adult cohort.

See **Table 1**, for the definition of the different levels of evidence.

BD: bipolar disorder; MDD: major depressive disorder; SSRIs: selective serotonin reuptake inhibitors; SUD: substance use disorder; TCAs: tricyclic antidepressants.

only 1 week of starting lithium therapy, which makes the results of this study difficult to interpret. The 6-month, double-blind, placebo-controlled comparison trial of lithium monotherapy to the combination of lithium plus valproic acid described previously (see section on lithium) reported a trend toward improvement in the substance use outcomes but failed to establish a significant difference between the 2 treatment groups.[28]

Adding valproic acid to lithium is a first-choice treatment recommendation for cannabis and cocaine abuse disorders comorbid with BD, whereas valproic acid monotherapy or valproic acid added to other ongoing medications other than lithium are second-choice recommendations.

Antidepressants

The available literature focused on treating MDD comorbid with SUDs.

Tricyclic antidepressants (TCAs).

AMITRIPTYLINE. A double-blind, head-to-head RCT was conducted of amitriptyline (100 to 150 mg/d; n = 20) and mirtazapine (30 to 60 mg/d; n = 24) in treating MDD patients with AUD who previously had been detoxified with a tapering regimen of diazepam. Both agents demonstrated efficacy in treating the mood disorder as well as in significantly reducing alcohol craving ($P < .01$).[36] Although there was no statistically significant difference between the 2 agents ($P = .275$), mirtazapine was better tolerated.

DESIPRAMINE. Desipramine was assessed in a placebo-controlled RCT of 71 alcohol-dependent patients. A subset of 28 of these patients also had secondary MDD.[37] Desipramine (200 mg/d) demonstrated efficacy in prolonging abstinence compared with placebo for both depressed and non-depressed subjects ($P = .03$).

Desipramine was not effective in treating cocaine and opiate dependence in 3 double-blind, placebo-controlled,

RCTs of MDD patients.[38-40] First, in a 12-week, double-blind, placebo-controlled, RCT comparing buprenorphine-maintained patients (mean = 15 mg/d; range, 8 to 24 mg/d) with lifetime MDD (desipramine, n = 30; placebo, n = 23) to never depressed (ND) patients (desipramine n = 44; placebo n = 23), the desipramine treatment (150 mg/d) increased the mean proportion of cocaine and opiate free-urines significantly for the ND group compared with the other groups ($z = -2.89$; $P = .003$).[38] However, the increase was not significant for the MDD group.

In the second double-blind, placebo-controlled RCT, 164 opioid- and cocaine-dependent patients were treated with desipramine (150 mg/d) or placebo in combination with either methadone (65 mg/d) or buprenorphine (12 mg/d) over 13 weeks.[39] When comparing the lifetime MDD group (n = 47) to the ND group (n = 117), the MDD group treated with desipramine and buprenorphine showed the least improvement in opioid-free urines ($z = 2.7$; $P < .008$) and desipramine did not reduce depressive symptoms more than placebo. Therefore, the authors concluded that combination of desipramine and buprenorphine is not indicated in depressed opioid-dependent patients.

Finally, a 12-week, double-blind, placebo-controlled RCT of desipramine (up to 300 mg/d) for MDD (n = 55) or dysthymia (n = 111) comorbid with cocaine dependence demonstrated that desipramine generated a significant antidepressant response, defined as at least a 50% reduction in the HRSD score from baseline, compared with placebo ($P < .05$). However, treatment groups did not differentiate on cocaine-dependence measures.[40]

In conclusion, desipramine has level 2 evidence, which is negative for cocaine and opiate use and therefore cannot be recommended to treat these conditions in MDD. However, desipramine has positive level 2 evidence and obtains a third-choice recommendation for the treatment of AUD in MDD by prolonging the period of abstinence.

IMIPRAMINE. In a 12-week, open-label trial of imipramine in MDD (n = 34) or dysthymia (n = 51) comorbid with AUD, 60 out of 85 patients completed a minimum adequate trial of imipramine (average dose of 263 mg/d).[41] Fifty-eight percent (n = 35) were responders based on a global rating of "much improved" on the Clinical Global Impression (CGI) scale and either abstinence or a marked reduction in drinking, with minimal functional impairment. Patients who responded to the open trial were eligible for a 6-month, double-blind, placebo-controlled RCT in which they were randomly assigned to remain on imipramine or switch to placebo. The proportion of relapse (alcohol or depression) was lower with imipramine (4 out of 13) compared with placebo (7 out of 10), but did not reach significance ($P = .09$).

Another 12-week, double-blind, placebo-controlled RCT of imipramine evaluated 69 patients with MDD, dysthymia, or depressive disorder NOS comorbid with AUD.[42] Imipramine treatment (n = 27) was associated with a significant improvement in depression compared with placebo (n = 29), although the magnitude of improvement was modest ($P \leq .05$). Imipramine responders had fewer heavy drinking days at end point. Therefore, imipramine treatment obtains a third-choice recommendation to support its use in treating AUD comorbid with MDD, with the cautionary note that the effect might be modest.

A 12-week double-blind, placebo-controlled RCT comparing imipramine (mean = 150 ± 65 mg/d; n = 59) to placebo (n = 54) as a treatment for cocaine abuse in depressed and non-depressed patients demonstrated that the proportion of favorable response (defined as at least 3 consecutive, urine-confirmed, cocaine-free weeks) was greater among depressed patients taking imipramine (26%, 10/38) than placebo (13%, 4/31), but did not reach statistical significance ($P < .19$).[43]

In an 8-week placebo-controlled, double-blind RCT evaluating imipramine hydrochloride (mean: 139.4 mg/d) for treating depression in methadone-maintained opiate addicts (N = 46), patients receiving either imipramine or placebo experienced a substantial reduction of depressive symptoms but no significant difference was found between the groups.[45] However, imipramine demonstrated efficacy in treating opiate use comorbid with MDD in a more recent 12-week, double-blind, placebo-controlled RCT involving 137 MDD patients receiving methadone hydrochloride maintenance treatment. Of the original 137 patients, 84 completed a minimum adequate trial of at least 6 weeks.[44] On measures of depression response (defined as a CGI depression improvement score of at least "much improved") and HRDS total score, there was a robust effect of imipramine compared with placebo ($P \leq .001$). Fifty-seven percent (24/42) of patients receiving imipramine were rated as responders (defined as a depression response and at least a 75% reduction from baseline in self-reported substance use) compared with 7% (3/42) receiving placebo ($P < .001$).

TABLE 3

Pharmacologic treatment recommendations for mood disorders comorbid with SUDs

Substance	MDD	Bipolar disorder
Alcohol	*First choice:* Mirtazapine Add-on naltrexone or alone Add-on naltrexone to sertraline[a]	*First choice:* Add-on naltrexone
	Second choice: Add-on disulfiram	*Second choice:* Add-on lamotrigine or alone Add-on valproic acid or alone Add-on disulfiram
	Third choice: Valproic acid Amitriptyline Desipramine Imipramine Escitalopram Memantine	*Third choice:* Add-on gabapentin Add-on topiramate Lithium
	Not recommended: Fluoxetine[b] Lithium Sertraline Nefazodone (withdrawn from the market)	*Not recommended:* Add-on quetiapine or alone
Cannabis	*First choice:* none	*First choice:* Add-on valproic acid to lithium
	Second choice: none	*Second choice:* Lithium Add-on valproic acid or alone
	Third choice: none	*Third choice:* none
	Not recommended: Fluoxetine[b]	*Not recommended:* none
Cocaine	*First choice:* none	*First choice:* Add-on valproic acid to lithium
	Second choice: none	*Second choice:* Add-on lamotrigine or alone Lithium Add-on valproic acid or alone Add-on quetiapine or alone Add-on risperidone or alone Add-on citicoline
	Third choice: Add-on risperidone or alone	*Third choice:* none
	Not recommended: Carbamazepine Desipramine Imipramine Nefazodone Fluoxetine Lithium	*Not recommended:* Carbamazepine
Heroin	*First choice:* none	*First choice:* none
	Second choice: none	*Second choice:* Methadone
Heroin (continued)	*Third choice:* Add-on buprenorphine or alone	*Third choice:* none
	Not recommended: none	*Not recommended:* none
Opiate	*First choice:* none	*First choice:* none
	Second choice: none	*Second choice:* none
	Third choice: Add-on imipramine to methadone	*Third choice:* none
	Not recommended:	*Not recommended:*
	Add-on fluoxetine to methadone Add-on sertraline to methadone maintenance for opiate-dependent patients	none
Amphetamine	*First choice:* none	*First choice:* none
	Second choice: none	*Second choice:* Add-on quetiapine or alone
	Third choice: none	*Third choice:* none
	Not recommended: none	*Not recommended:* none
Methamphetamine	*First choice:* none	*First choice:* none
	Second choice: none	*Second choice:* Add-on quetiapine or alone Add-on risperidone or alone
	Third choice: none	*Third choice:* none
	Not recommended: none	*Not recommended:* none
Polysubstance	*First choice:* none	*First choice:* none
	Second choice: none	*Second choice:* Switch from current antipsychotic(s) + add-on aripiprazole
	Third choice: none	*Third choice:* none
	Not recommended specifically for opiate plus cocaine polysubstance: Add-on desipramine to buprenorphine maintenance for opiate-dependent patients Add-on desipramine to methadone maintenance for opiate-dependent patients	*Not recommended:* none

[a]Not recommended for patients age >55.
[b]Can be a possible choice for adolescents and young adults.

First-choice recommendation: level 1 or level 2 evidence plus clinical support for efficacy and safety; second-choice recommendation: level 3 evidence or higher plus clinical support for efficacy and safety; third-choice recommendation: level 4 evidence or higher plus clinical support for efficacy and safety; not recommended: level 1 or level 2 evidence for lack of efficacy.

MDD: major depressive disorder; SUD: substance use disorder.

Selective serotonin reuptake inhibitors (SSRIs).

ESCITALOPRAM. In a 26-week, double-blind, head-to-head RCT, 80 AUD patients with comorbid MDD were randomized to escitalopram (20 mg/d) or memantine (20 mg/d) and assessed with the Alcohol Use Disorders Identification Test (AUDIT), AUDIT Quantity-Frequency, and Obsessive Compulsive Drinking Scale (OCDS), and with depressive symptoms measured by the Montgomery-Åsberg Depression Rating Scale. Both escitalopram and memantine groups improved significantly from baseline on all measures ($P < .0001$), with no significant difference on outcome measures between the groups.[46,47] However, these results are difficult to interpret because of the absence of a placebo group and because none of the treatments studied have been shown to be efficacious against placebo in the treatment of AUD comorbid with MDD. Because neither of the 2 treatments under study could be considered an *active* comparator, we are attributing third-choice treatment recommendations for these 2 compounds.

FLUOXETINE. In a 12-week, placebo-controlled RCT of fluoxetine (up to 60 mg/d) for 101 AUD patients who were not selected on the basis of comorbid MDD, fluoxetine treatment had no significant effects on alcohol consumption.[48] However, it significantly reduced the HRSD scores compared with placebo ($P < .01$) among the subgroup of patients with current MDD. In another 12-week, double-blind, placebo-controlled RCT, 51 patients diagnosed with comorbid MDD and AUD were randomized to receive fluoxetine (20 mg/d; n = 25) or placebo (n = 26).[49,51] The improvement in depressive symptoms and the decrease in total alcohol consumption were significantly greater in the fluoxetine group ($P < .05$) than in the placebo group ($P < .03$).

In a 12-week, open-label, acute-phase pilot study of 13 adolescents with comorbid AUD and MDD, patients received open-label fluoxetine (20 mg) and were followed by comprehensive assessments conducted at 1, 3, and 5 years. Fluoxetine demonstrated within-group efficacy for decreasing drinking and depressive symptoms ($P \leq .08$ and $P \leq .001$, respectively). The study also suggested that fluoxetine was a safe medication in this population.[52-54] However, results of a 12-week, double-blind, placebo-controlled RCT of fluoxetine vs placebo in that same adolescent population with comorbid MDD and AUD (N = 50), demonstrated no significant superiority of fluoxetine for treating either the depressive symptoms or the alcohol use behaviors compared with placebo.[55]

A recent 12-week, double-blind, RCT evaluating efficacy of fluoxetine vs placebo in adolescents and young adults (21.1 ± 2.4 years; N = 70) with comorbid MDD and cannabis use disorder failed to demonstrate greater efficacy of fluoxetine (n = 36) compared with placebo (n = 34) for treating either depressive symptoms or cannabis-related symptoms.[56]

Two small studies showed lack of efficacy for fluoxetine in cocaine use comorbid with MDD.[57,58] First, data on the efficacy of fluoxetine vs placebo in 51 alcohol-dependent patients with MDD presented above were reanalysed[49] in a post-hoc analysis. Seventeen patients with a concurrent diagnosis of cocaine abuse were compared with 34 depressed alcoholics who did not abuse cocaine.[57] The cocaine abuse subsample showed significantly worse outcomes on depressive scale scores and on multiple measures of alcohol consumption. In this subset of 17 cocaine abusers and depressed chronic alcoholics, there were no statistically significant differences in cocaine use, alcohol use, or improvement of depressive symptoms between patients treated with fluoxetine (n = 8) or placebo (n = 9). Within-group differences were not encountered either. The authors concluded that despite the small sample size limiting the significance of the results, these findings suggest that fluoxetine is not useful in treating depression or alcohol use in depressed patients with concomitant cocaine abuse. The second trial studied the efficacy of fluoxetine and individual cognitive-behavioral psychotherapy targeting both cocaine use and depression in 32 cocaine-dependent patients with comorbid depression.[58] Depressive symptoms improved and cocaine-positive urine testing decreased during the study period, but differences between fluoxetine and placebo were not significant.

Add-on fluoxetine or placebo to methadone maintenance treatment has shown no difference either in opioid use or in depressive symptoms for the treatment of comorbid MDD and opioid dependence.[50,59]

In summary, fluoxetine proved efficacious only in 1 of 2 double-blind, placebo-controlled RCTs for patients with MDD and AUD. Given the opposing results of these studies, we cannot recommend its use as a first-choice treatment. In addition, fluoxetine cannot be recommended for treating cannabis, cocaine, or opiate use disorders comorbid with MDD in adults and youths.

NEFAZODONE. Nefazodone has been withdrawn from the market because of its association with liver complications. Therefore, the following description of study results

is only of academic interest. At least 1 open-label[60] and 2 double-blind, placebo-controlled RCTs[61,62] of nefazodone treatment for MDD comorbid with AUD support a level 1 of evidence. The positive and significant results on reduction in heavy drinking days and in total drinks in the nefazodone group compared with the placebo group would have supported a first-choice recommendation in the treatment of comorbid AUD with MDD.

SERTRALINE. Sertraline often has been studied in the treatment of AUD comorbid with a mood disorder; however, the results are not convincing.[64-68] A recent, 14-week, double-blind, placebo-controlled RCT compared sertraline (200 mg/d; n = 40), naltrexone (100 mg/d; n = 49), combination sertraline plus naltrexone (n = 42), and double placebo (n = 39) for treating co-occurring MDD and AUD. Results showed no difference in the level of abstinence or delay before relapse to heavy drinking among sertraline alone, naltrexone alone, sertraline plus naltrexone, and placebo.[69] However, the sertraline plus naltrexone combination produced a higher alcohol abstinence rate (P = .001), a higher rate of patients who did not drink heavily (P = .001) and a longer delay before relapse to heavy drinking (P = .003) compared with the other 3 groups combined.[69]

One 12-week, double-blind, placebo-controlled RCT of sertraline (mean: 169 mg/d; standard deviation [SD] = 71.5 mg/d; n = 47) compared with placebo (n = 48) evaluated its use in syndromally defined depressive disorders among non-abstinent, methadone-maintained, opiate-dependent patients (N = 95).[70] There was no main effect of sertraline on either depression or substance use outcomes.

Therefore, sertraline alone or as an add-on to methadone obtains a *negative* level 2 of evidence respectively for treating alcohol or opiate SUD in MDD patients, and a classification among the "not recommended" treatments for these conditions, whereas the combination of naltrexone plus sertraline has a first-choice recommendation to support its use in treating comorbid AUD and MDD.

MIRTAZAPINE. As previously discussed in the amitriptyline section, mirtazapine was studied in a head-to-head, double-blind RCT of amitriptyline (100 to 150 mg/d; n = 20) and mirtazapine (30 to 60 mg/d; n = 24) in the treatment of AUD in MDD patients. Although there was no statistically significant difference between amitriptyline and mirtazapine (P = .275), mirtazapine was better tolerated.[36] The effectiveness and tolerability of mirtazapine in treating MDD comorbid with AUD (N = 184) also had been studied in an open-label, naturalistic, multicenter treatment trial.[71] This study showed a statistically significant reduction in scores on the $HRSD_{17}$ (P < .0001), the OCDS (P < .0001), and the Visual Analog Scale for Craving (P < .0001), from baseline to endpoint (week 8). Adverse events related to mirtazapine were observed in ≥10% of patients in this study. Thus, mirtazapine is a first-choice recommendation in treating AUD comorbid with MDD.

Antipsychotics

Aripiprazole. Aripiprazole was studied in a small, 12-week, open-label study of polysubstance abuse (alcohol, n = 17; cocaine, n = 9; opioids, n = 3; and cannabis, n = 3) in BD patients (N = 19).[72] Aripiprazole improved mood (depressive and manic) symptoms (P = .002 and P = .021, respectively), decreased alcohol (P = .003) and cocaine craving (P = .014), and reduced the dollars spent per week for alcohol (P = .042). However, number of days of alcohol or cocaine use per week and the number of cocaine-positive urine screens were not significantly reduced.

Quetiapine. Whereas some open-label trials of quetiapine reported good outcomes,[73,74] RCTs did not demonstrate efficacy of quetiapine in BD comorbid with AUD. For example, a small open-label study of the safety and efficacy of quetiapine (300 to 800 mg/d) in treating AUD in patients with dual diagnosis (including a subgroup of 16 BD patients) demonstrated a significant decrease in alcohol consumption, craving, and mood disorder symptoms intensity. However, results specific to the BD cohort alone were not available.[74] Two large, 12-week, double-blind placebo-controlled RCTs examined the role of add-on quetiapine (300 to 800 mg/d) in treating comorbid AUD in BD (N = 291) and found no benefit on measures of AUD.[75,76]

One 20-week, double-blind, head-to-head RCT comparing quetiapine (mean dose: 301.9 mg/d; n = 42) and risperidone (mean dose: 3.1 mg/d; n = 38) for cocaine or methamphetamine use in BD found positive improvements in drug craving (P < .0005) and in overall drug use (P = .03) in both treatment arms.[77] Moreover, a positive outcome on mood, cocaine craving, and cocaine use also was reported in 2 other studies of quetiapine in patients with BD comorbid with cocaine[78,79] or stimulant use.[78]

Admittedly, the absence of a placebo arm in these studies make the interpretation of these results more difficult. Therefore, second-choice recommendation

was assigned to the add-on use of quetiapine in treating cocaine, amphetamines, and methamphetamines in BD.

Risperidone. A small, open-label, naturalistic study of risperidone treatment (1.18 mg/d) in cocaine-dependent BD (n = 9) or MDD (n = 6) patients with or without psychotic features, found that risperidone was safe and well-tolerated and may decrease cocaine craving and use.[80] Six out of 9 BD patients and all 6 MDD patients had comorbid AUD, but no specific results were obtained on AUD outcomes. As previously reported in the section on quetiapine, both risperidone (mean dose: 3.1 mg/d; n = 38) and quetiapine (mean dose: 301.9 mg/d; n = 42) was associated with decreased drug craving ($P < .0005$) and overall drug use ($P = .03$) in a 20-week, double-blind RCT in BD patients with comorbid cocaine or methamphetamine use.[77]

A second-choice recommendation is assigned for the use of add-on or monotherapy risperidone for cocaine or methamphetamine SUD comorbid with BD because of the absence of a placebo-controlled study. Only a third-choice recommendation can be assigned to the use of add-on or monotherapy risperidone for cocaine use disorder comorbid with MDD.

Other agents

Buprenorphine. A 12-month, open-label, retrospective study examined buprenorphine (average dose: 7.9 mg/d) for heroin dependence comorbid with MDD (n = 61) or other psychiatric disorders (generalized anxiety disorder; personality disorders, antisocial-borderline; schizophrenia; SUD without overt psychiatric comorbidity [N = 145]). Buprenorphine demonstrated a higher retention rate (at least $P \leq .006$) and a trend toward a decreased risk of illicit opioid use ($P \leq .06$) in the MDD subgroup compared with each of the other subgroups of patients.[81]

Citicoline. A 12-week, placebo-controlled RCT of add-on citicoline (up to 2,000 mg/d) was conducted in 44 outpatients with a history of mania or hypomania and cocaine dependence.[82] Citicoline use was associated with significantly lower probability of a cocaine-positive urine ($P = .026$) compared with placebo but no significant difference was observed on mood symptoms. A second-choice recommendation is assigned because of the lack of statistical difference on mood symptoms between the treatment and placebo arms. A larger study of citicoline in patients with BD I and cocaine dependence is ongoing, as well as studies on methamphetamine and cannabis use to establish the efficacy of citicoline for these SUDs.

Disulfiram. Early clinical reports suggested that disulfiram at a higher dose than those currently used could increase some psychiatric symptoms, including delirium, depression, anxiety, mania, and psychosis.[83] More recent studies have shown no indication of psychotic symptoms worsening for patients with a dual diagnosis of AUD and psychiatric disorders, including BD.[84-87,89,90] Moreover, a 12-week RCT of disulfiram (250 mg/d) vs naltrexone or placebo for the treatment of AUD comorbid with or without psychotic spectrum disorder (N = 251), including BD (n = 48) or MDD (n = 150) showed a significant decrease in the number of drinking days per week ($P = .02$) and number of consecutive days of abstinence ($P = .04$) for the disulfiram treatment group compared with the no disulfiram treatment group.[88] However, disulfiram treatment alone was not superior to naltrexone or to disulfiram plus naltrexone. Finally, practical and safety issues surrounding the use of disulfiram warrant that we attribute a second-choice treatment recommendation for this agent.

Memantine. A 26-week, double-blind, head-to-head RCT of memantine (20 mg/d; n = 40) and escitalopram (20 mg/d; n = 40) for treating MDD comorbid with AUD found that the levels of depression, anxiety, and alcohol consumption ($P < .0001$) and craving ($P < .0001$) were significantly reduced in both groups combined. There was no significant difference between the memantine and escitalopram groups.[46,47] These results are difficult to interpret because of the absence of a placebo group and because none of the treatments studied have been shown to be efficacious against a placebo in a study on treating AUD comorbid with MDD. In other words, none of the 2 treatments under study could be considered an active comparator. Therefore, we are attributing only a third-choice recommendation for these 2 compounds.

Methadone. A small, open-label study involving only 27 BD patients reported benefits and good tolerability of methadone for treating heroin addiction.[91] Although BD patients required a higher dose of methadone than non-psychiatrically ill patients, and this substitution with methadone contributed to improvement in their social, legal, and physical stability, it did not contribute to improving the bipolar illness per se. No data are available concerning MDD and comorbid SUDs.

Naltrexone. In a retrospective study of psychiatric patients with MDD or BD comorbid with AUD, naltrexone was shown to be effective in reducing alcohol

TABLE 4
Criteria for level of evidence[a] and line of treatment[b] for psychotherapies and psychosocial treatments

Evidence level	**Criteria**
Level 1	At least 2 RCTs with adequate sample sizes, preferably placebo-controlled, and/or meta-analysis with narrow confidence intervals
Level 2	At least 1 RCT with adequate sample size and/or meta-analysis with wide confidence intervals
Level 3	Non-randomized, controlled prospective studies or case series or high quality retrospective studies
Level 4	Expert opinion/consensus
Line of treatment	**Criteria**
First choice	Level 1 or level 2 evidence, plus clinical support[c]
Second choice	Level 3 evidence or higher, plus clinical support[c]
Third choice	Level 4 evidence or higher, plus clinical support[c]

[a]Note that level 1 and 2 evidence refer specifically to treatment studies in which randomized comparisons are available. Recommendations involving epidemiological or risk factors primarily arise from observational studies, hence the highest level of evidence is usually level 3. Higher-order recommendations (eg, principles of care) reflect higher-level judgment of the strength of evidence from various data sources, and therefore are primarily level 4 evidence.
[b]A first-choice treatment represents a balance of efficacy, tolerability, and clinical support. Second-choice and third-choice treatments are reserved for situations where first-choice treatments are not indicated or cannot be used, or when first-choice treatments have not worked.
[c]Clinical support refers to application of expert opinion to ensure that evidence-supported interventions are realistic in clinical practice. Therefore, treatments with higher levels of evidence may be downgraded to lower lines of treatment due to clinical issues such as side-effect or safety profile.

RCT: randomized controlled trial.

use.[92] An open-label study showed a decrease in alcohol use, but also an improvement of depressive symptoms in depressed alcoholic patients.[93] In a recent 12-week double-blind placebo-controlled RCT of add-on naltrexone (50 mg/d) or placebo in 50 adult outpatients with BD and AUD, naltrexone showed a trend ($P < .10$) toward a greater decrease in drinking days (binary outcome) and alcohol craving.[97] As discussed in the section on disulfiram, a 12-week, double-blind, placebo-controlled RCT of naltrexone (50 to 250 mg/d) or placebo compared open randomization to disulfiram or no disulfiram, was conducted in 198 BD or MDD patients out of 251 with comorbid diagnoses of psychiatric disorders with alcohol abuse.[88] The study showed a significant increase in the number of abstinent days and in the number of heavy drinking days for the naltrexone treatment group compared with the placebo group. As previously mentioned, this study also showed a significant increase in the number of abstinent days and in the number of total heavy drinking days for the disulfiram treatment group compared with the no disulfiram treatment group. The subgroup of treated patients with both medications (naltrexone plus disulfiram) did not show significantly better outcomes in the number of abstinent days and in the number of total heavy drinking days compared with those treated with disulfiram or naltrexone alone.[87,88] In a 12-week, double-blind, placebo-controlled RCT of add-on sertraline (100 mg/d) to naltrexone (50 mg/d) or placebo in patients age ≥55 (average age: 63.4) with comorbid MDD and AUD, there was no evidence for an added benefit of naltrexone in combination with sertraline compared with placebo.[94]

As previously described in the section on sertraline, a 14-week, double-blind, placebo-controlled RCT comparing sertraline (200 mg/d; n = 40), naltrexone (100 mg/d; n = 49), combination sertraline plus naltrexone (n = 42), and double placebo (n = 39) for treating co-occurring depression and alcohol dependence, demonstrated that the sertraline plus naltrexone combination produced a higher alcohol abstinence rate ($P = .001$), a higher rate of patients who did not drink heavily ($P = .001$) and a longer delay before relapse to heavy drinking ($P = .003$) compared with the other 3 groups combined.[69] Therefore, the combination of naltrexone plus sertraline has a first-choice recommendation for the treatment of comorbid AUD with MDD.

Psychotherapies and psychosocial treatments

Psychotherapeutic and psychosocial treatments are understandably impossible to assess with double-blind and placebo-controlled studies. Therefore, for the pur-

TABLE 5
Level of evidence for psychotherapies and psychosocial treatments for the treatment of mood disorders comorbid with SUDs

Therapy	MDD	Bipolar disorder
CBT	Level 3: negative[104-106]	Level 2: negative[104,107] Integrated Group Therapy by Weiss: level 2[108-110]
MI	Level 2[111-114]	Level 3[111-113]
CBT + MI	Level 2: negative[115-117]	Level 2: negative[116,117]
ACT	Level 3[118,119,123]	Level 2[118,119,123,125]
CM	Level 2[38,114,120-122]	Level 3[114,120-122]

See **Table 4**, for the definition of the different levels of evidence.

ACT: assertive community treatment; CBT: cognitive-behavioral therapy; CM: contingency management; MI: motivational therapy; SUD: substance use disorder.

pose of this section, the CANMAT recommendations criteria were chosen for psychotherapeutic treatments of MDD[99] (**TABLE 4**).

As stated earlier in this article, most of the studies focus on a given SUD comorbid with a non-specific mental disorder, often mixing schizophrenia with mood disorders and presenting the results for the whole sample. This makes it difficult to derive conclusions about the efficacy of the treatment for a specific mood disorder, such as MDD or BD. Therefore, it is difficult to attribute a level 1 of evidence to any of these treatments.

Our review included all RCTs or non-randomized trials of any psychosocial interventions for MDD or BD comorbid with SUDs, which utilized substance use as an outcome measure. Studies were classified into the following categories: cognitive-behavioral therapy (CBT), motivational therapy (MI), combination of CBT and MI (CBT+MI), assertive community treatment (ACT), and contingency management (CM).

Other psychotherapies or psychosocial interventions such as family interventions, residential treatment, intensive outpatient rehabilitation, and legal intervention were not included because of the paucity of studies, non-specificity of the mental health comorbid disorder, or the specific and restrictive type of patients being studied, such as the homeless. Moreover, 2 major projects (MATCH [Matching Alcoholism Treatment to Client Heterogeneity] and the VA Effectiveness Study) conducted during the 1990s on SUDs with large cohorts of participants (with a probable proportion of MDD or BD) failed to demonstrate that patient characteristics and treatment process elements respectively, constitute mediators and moderators of change in drinking and drug use following treatment.[99]

Recent reviews on psychosocial treatments[100-102] and 1 meta-analysis also were considered by the Cochrane Schizophrenia Group[103] studying comorbid severe mental disorder and SUDs. These papers did not focus specifically on mood disorders, and SUD outcomes were not always evaluated, making it difficult to extract pertinent results for MDD and BD.

The summary of our review of the literature and attribution of the level of evidence for each therapy is presented in **TABLE 5**.[38,104-123]

CBT. Out of the 3 studies we could locate, none demonstrated superiority of CBT on SUD outcomes compared with the alternate treatment, be it the 12-step group therapy[104-106] or simple medical monitoring.[107] The integrated group therapy developed by Weiss and colleagues[108-110] based on CBT components, has been studied in a pilot study and 2 separate RCTs (N = 168) but all by the same group of investigators. This technique has been developed specifically for BD patients with a comorbid SUD, and consists of 12 to 20 group sessions, which was compared with either group drug counseling or no treatment. Results consistently indicated a superiority of that treatment in terms of decreased drug use and increased total and consecutive abstinent days, even at 8-month follow-up. This specific treatment fulfills criteria for level 2 evidence, and provides positive results in the BD plus SUD patients. However, longer-term studies are needed, and replication from other groups of investigators are warranted before we could attribute a level 1 evidence rating.

MI. Three large RCT studies, each with >120 patients, evaluated the impact of 1 MI session (2 studies) or group MI combined with contingency strategies (1 study), on SUD outcomes in patients with a comorbid

mental disorder, such as MDD, in proportions of up to 56%.[111-113] However, no study of MI in BD comorbid with a SUD with >10 patients could be found. Overall, MI partially decreased drug consumption, particularly in polysubstance abusers, but only at 3-month follow-up.[111,112] In another large study of 120 patients with 63% suffering from comorbid MDD and AUD, a small but significant decrease in alcohol consumption, without changing alcohol abuse severity overall was reported.[113] Finally, group MI coupled with contingency strategies increased the duration of abstinence and the proportion of negative drug screens (cocaine, heroin, cannabis), compared with group supportive therapy.[114] Therefore, MI appears to show a very small benefit in the short-term, but not on global SUD outcomes, and especially not on long term. This is reinforced by a complete Cochrane meta-analysis[103] of all MI studies in SUDs comorbid with any severe mental illness, concluding that MI did not reduce the rate of loss to follow-up.

MI plus CBT. Three studies have combined MI and CBT.[115-117] In the first study, 97 MDD patients with comorbid alcohol and/or cannabis use disorder were randomized to either 1 session of brief intervention, or brief intervention followed by 9 sessions of individual sessions of MI plus CBT, delivered either by computer or a therapist.[115] MI plus CBT resulted in better outcomes for cannabis use. Both brief intervention and MI plus CBT improved AUD, but these results from the 2 therapies were not statistically different. Finally, a 10-session MI plus CBT intervention among 65 patients suffering from a psychotic mood disorder with comorbid SUDs over a period of 12 months, demonstrated short-term benefits over treatment as usual (TAU), but failed to show long-term superiority over TAU.[117] Therefore, the assessment in this paper does not suggest a significant advantage with MI plus CBT.

ACT. Two studies[118,119,124] by the same team compared ACT with standard case management for co-occurring severe mental disorder and active SUD, in a total of 241 patients with MDD with bipolar features, or BD. Whereas the older study demonstrated a decrease in alcohol severity and in drug and alcohol use of up to 3 years in 51 BD patients, the more recent study failed to find a group difference for substance outcomes.[125]

CM. Among 5 recent studies comparing CM with non-CM, 2 large studies were done in MDD.[38,114,120-122] The first included patients with comorbid cocaine SUD and the second included patients with comorbid cocaine, heroin, or cannabis SUD.[38,114] A 12-week RCT compared 4 treatment groups (desipramine plus CM; desipramine plus non-CM; placebo plus CM; and placebo plus non-CM) for cocaine abuse in patients with buprenorphine-maintained MDD vs never depressed patients.[38] CM significantly improved drug-free urine proportions, more for patients with MDD than non-depressed patients. Finally, as mentioned earlier, group MI coupled with CM increased the length of abstinence periods and proportion of negative drug screens (cocaine, heroin, cannabis) compared with group supportive therapy.[114] Three other studies[120-122] demonstrated some improvement in alcohol or drug outcomes, but the MDD or BD arms contained <10 patients, making this difficult to conclude.

In summary, many of the psychotherapeutic interventions have been studied in a variety of study designs, often mixing clinical populations. This makes the process of assessing clinical efficacy using evidence-based criteria quite difficult. In fact, the most recent Cochrane review on the subject examined 25 RCTs and concluded that it was impossible to rule in favor of any specific psychosocial treatment, because of a large array of methodological differences and difficulties impeding data pooling as well as interpretation.[103]

Clearly, evidence from RCTs for psychosocial treatment is lacking in comorbid mood disorders and SUDs, but clinicians facing the task of treating these difficult cases need some guidance. When considering the programmatic nature of these treatments, Mueser et al[126] suggested that quasi-experimental evidence could be considered sufficient to define evidence-based practices for the purposes of clinical implementation for persons with mental illness.[127,128]

CONCLUSIONS

The field of mood disorders comorbid with SUDs is in need of large double-blind, placebo-controlled RCTs with well-characterized patients suffering from a specific SUD. The lack of evidence stemming from such high quality and specificity studies prevents us from making clinical recommendations for most of these frequent clinical occurrences of mood disorders comorbid with SUDs. The following suggestions of treatments are based solely on the limited number of studies of variable quality available. It is important to underline that these recommendations are not guidelines, but only

suggestions based on the limited data available, safety, tolerability, and clinical support.

TABLE 3 summarizes the recommendations we could arrive at for the pharmacologic treatment of the most frequent SUDs studied. The available data allows us to generate first-choice recommendations for AUD comorbid with MDD and only third-choice recommendations for cocaine, heroin, and opiate SUD comorbid with MDD. No recommendations were possible for cannabis, amphetamines, methamphetamines, or polysubstance SUD comorbid with MDD. First-choice recommendations were possible for alcohol, cannabis, and cocaine SUD comorbid with BD and only second-choice recommendations for heroin, amphetamine, methamphetamine, and polysubstance SUD comorbid with BD. No recommendations were possible for opiate SUD comorbid with BD.

Finally, although they are an essential component of the overall treatment of comorbid SUDs with mood disorders, psychotherapies are in need of further well-designed studies to properly assess their potential role in specific SUDs comorbid with mood disorders.

The field of SUDs comorbid with psychiatric conditions and with mood disorders in particular, has been difficult to study as demonstrated by the small number of available studies. Moreover, a better neurobiologic understanding of these co-occurring or comorbid disorders is needed to guide research toward better targeted treatments that are more likely to generate positive efficacy results. In the meantime, clinicians may derive benefit from considering the available information and recommendations summarized in this manuscript. ■

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