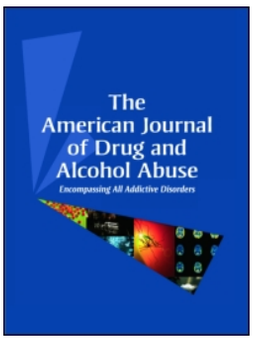

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Management of comorbid bipolar disorder and substance use disorders

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ABSTRACT

Background: The comorbidity of substance use disorders (SUDs) in bipolar disorder is among the highest in psychiatric disorders. Evidence-based controlled psychosocial or pharmacological interventions trials, which may guide treatment decisions, have not been systematically reviewed. *Objective*: To present a narrative review of the public health and clinical significance of this condition, including diagnostic and treatment implications, and to evaluate controlled trials conducted to date. *Methods*: Controlled trials reports in the English language were identified from multiple electronic databases and hand-searching bibliographies. We searched for treatment studies of bipolar disorder and comorbid SUDs (alcohol, cocaine, stimulants, opioid, tobacco, cannabis). Search period included all reports through September of 2016. We selected only randomized psychosocial studies or double-blind, placebo-controlled pharmacotherapy trials. We also reviewed reports of the public health and clinical significance and principle of managements of this condition. *Results*: We identified 16 treatment studies: 3 psychotherapy, and 13 pharmacotherapy trials. The following medications were evaluated: lithium carbonate, valproate, lamotrigine, topiramate, naltrexone, acamprosate, disulfiram, quetiapine, and citicoline. SUDs have substantial impact on the recognition and management of bipolar disorder. Integrated psychosocial interventions are helpful in decreasing substance abuse. Valproate and naltrexone may decrease alcohol use and citicoline may decrease cocaine use and enhance cognition. *Conclusions*: There is a very limited number of pharmacotherapy and an even smaller number of psychosocial interventions. Our review highlights the need for more research in this area and for larger, multisite studies with generalizable samples to provide more definite guidance for clinical practice.

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Introduction

Clinicians have long recognized the challenges of treating bipolar disorder, especially when it is associated with an alcohol or other substance use disorders (SUDs). These challenges pervade the clinical care process, from obscuring the diagnosis of the bipolar condition to interfering with medication and treatment adherence to ensuring stability of mood symptoms and preventing complications such as suicidal behavior. However, despite the high frequency of this comorbidity, there are no clearly effective interventions specifically designed to stabilize the mood symptoms and decrease alcohol and other drug use among these patients. The aims of this article are to present a narrative review of the clinical relevance and public health significance of bipolar disorder with comorbid SUDs and to review published treatment studies, with primary focus on medications trials, highlighting randomized controlled trials.

Method

Reports of randomized controlled trials in English language were identified from multiple electronic web-based searches of MEDLINE, PubMed, WEB OF SCIENCES databases, and hand-searching bibliographies of review articles. We searched for treatment studies using the following terms for bipolar disorder: "bipolar disorder" and "manic depression." We used the following terms for SUDs: "comorbid substance use disorders," "alcoholism," "cocaine," "stimulants," "opioid," "cannabis," and "tobacco." We used the following terms for intervention trials: "clinical trials," "pharmacotherapy," "dual diagnosis trials, anticonvulsants, atypical antipsychotics, mood stabilizers, divalproex sodium, topiramate, carbamazepine, gabapentin, lamotrigine, lithium carbonate, aripiprazole, quetiapine, olanzapine, risperidone, naltrexone, nalmefene, acamprosate, and disulfiram, psychotherapy, counseling." We combined searches for each of the three areas (i.e., bipolar disorder + each of the

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Table 1. Placebo-controlled trials in BPD and alcohol and cocaine use disorders.

Authors	*N*	Medication	Design	Substance	Disorder	Findings
Salloum et al. (69)	59	Valproic acid vs. placebo added to lithium	Randomized, placebo controlled	Alcohol	Bipolar I	Decrease in alcohol use but no difference in mood
Brown et al. (74)	115	Quetiapine vs. placebo	Randomized, placebo controlled	Alcohol	Bipolar I and II	Quetiapine improved depressive symptoms but not alcohol use
Brown et al. (76)	50	Naltrexone vs. placebo	Randomized, placebo controlled	Alcohol	Bipolar I and II	Tends toward reductions in alcohol use and improved mood
Stedman et al. (75)	362	Quetiapine vs. placebo	Randomized, placebo controlled	Alcohol	Bipolar I	CGI, but no other outcomes, favored quetiapine
Tolliver et al. (82)	33	Acamprosate vs. placebo	Randomized, placebo controlled	Alcohol	Bipolar I and II	No differences in alcohol use but positive effects on some secondary analyses
Sylvia et al. (71)	12	Topiramate	Randomized, placebo controlled	Alcohol	Bipolar I and II	Worse alcohol outcome in the topiramate group
Brown et al. (76)	90	Quetiapine vs. placebo	Randomized, placebo controlled	Alcohol	Bipolar I and II	No significant differences in alcohol use
Brown et al. (83)	44	Citicoline vs. placebo	Randomized, placebo controlled	Cocaine	Bipolar I and II	Less likely to have positive urine, improved declarative memory
Brown et al. (70)	120	Lamotrigine vs. placebo	Randomized, placebo controlled	Cocaine	Bipolar I and II	No differences in cocaine-positive urine, less reported money spent on cocaine
Brown et al. (84)	130	Citicoline vs. placebo	Randomized, placebo controlled	Cocaine	Bipolar I and II	Less likely to have positive urine on citicoline

substance use terms + each of the treatment terms). Search period included all reports published prior to September 2016. We selected for this review only randomized psychosocial studies or double-blind placebo-controlled pharmacotherapy trials (see Table 1). To provide a broader context for this comorbidity, we also reviewed selected reports of the public health and clinical significance and principle of managements of this high-risk comorbid condition.

Prevalence and clinical significance

The high association of bipolar disorder with alcoholism and other SUDs has been consistently reported by epidemiological surveys and clinical studies. The Epidemiological Catchment Area Study, a large survey of major psychiatric disorders in five major metropolitan areas in the United Stated found that, with the exception of antisocial personality disorder, bipolar disorder had the highest rate of SUDs compared to any other major psychiatric disorders (1). Several subsequent studies have confirmed and expanded on that finding. For example, respondents with mania were found to be 14 times more likely to have drug dependence and 6 times more likely to have alcohol dependence over the past 12 months by a large epidemiological survey of a representative sample of over 42,000 respondents in the United States of America (USA) (2). A recently published, comprehensive, population-based cohort study of the prevalence of SUD among Danish population analyzed the data of a total of 463,003 patients (3). That study reported a prevalence of a lifetime SUD of almost one-third (32%) in patients with bipolar disorder. Alcohol use disorder accounted for 25% of the prevalence rate of the SUDs. On the other hand, respondents with SUDs also have a higher lifetime rate of mania (3.7–13.4%) and hypomania (3.7–13.4%) (4) compared to the general population. The latest large epidemiological survey reported a significant association between 12-month drug-use disorder (according to the Diagnostic and Statistical Manual for Mental Disorder-5th Edition [DSM-5]) (5) and bipolar I disorder, with odd ratio of 1.5 (95% CI, 1.06–2.05) (6). Nicotine dependence is the most frequent SUD in bipolar disorder with lifetime rate of 83% and an estimated current smoking rate over 68% (7). Clinical studies have also highlighted the high frequency of substance abuse in bipolar disorder. The STEP-BD trial reported a lifetime rate of 32.2% and a current rate of 11.8% for alcohol use disorder and a lifetime rate of 21.7% and a current rate of 7.3% for drug-use disorders among a multisite clinical sample of 4000 patients (8). In a well-characterized clinical sample (9) of 89 patients, about 58% of bipolar I disorder and 39% of bipolar II disorders had any substance abuse. The most frequently reported substance of abuse for bipolar I and II, respectively, was alcohol (49% and 38.9%), followed by cannabis (20% and 5.6%), cocaine (11% and 5.6%), sedative hypnotic (7% and 5.6%), stimulants (5.6% and 5.6%), opioid (5.6% and 5.6%), and hallucinogen (2.8% and 5.6%). Almost one-third of bipolar I (28%) reported abusing two substances and 11% reported abusing three substances, while the rate in bipolar II was 17% for abusing two and 11% for abusing three substances. Although the sample size of that study

was relatively small and derived from a single site, it still provides an important indication on the frequency of this comorbidity in clinical practice.

Negative bidirectional relationship

There is a bidirectional negative impact of the presence of comorbidity on the bipolar disorder as well as on the SUD (10). The effects of SUDs on bipolar disorder are substantial with a negative impact on symptom presentation, manifestations, course, and treatment adherence. SUDs increase the severity of the clinical presentation of bipolar disorder with increased impulsive and suicidal behavior which usually results in increased rate of costly inpatient hospitalization (9,11–14). For example, increased severity of depressive symptoms was reported for females with bipolar-SUD comorbidity compared to either females with bipolar disorder without SUDs or to males with bipolar and comorbid SUD (15). SUDs impact significantly on the recognition and diagnosis of bipolar disorder contributing to delaying in initiating effective treatment and also impact on the overall management of bipolar disorder interfering with treatment and medication adherence (16).

On the other hand, bipolar disorder may confer a major vulnerability for developing SUDs and for relapse to SUDs. Also, adolescents with bipolar disorder are five times more likely to develop SUDs (17). Symptoms of bipolar disorder, especially during the manic or mixed states, most notably impulsiveness, increase the risk for substance abuse. Moreover, poorly controlled bipolar disorder impairs coping abilities to manage stress, which represents a key risk factor for relapse to substance abuse (18). For those individuals who are prone to self-medicate their distressing symptoms, bipolar disorder presents with a rich tapestry of symptoms varying from depression to anxiety to manic and psychotic symptoms, in addition to sleep difficulties, all of which may become a stimulus to self-medicate (10). Furthermore, longitudinal studies reported that patients have slower recovery, earlier onset, and more symptoms during follow-up when bipolar disorder occurs before the onset of alcoholism or cannabis use disorder compared to those when alcohol or cannabis use disorders occurring first, although this finding was stronger for alcohol than cannabis use disorder (19,20). Other evidence suggested that SUD, whether it is current or present in the past, was associated with lower likelihood of being in recovering/recovered status compared to those without a history of SUD and that younger age was associated with more difficult course (14).

High rates of multiple comorbidity

Furthermore, bipolar disorder is often multi-morbid with other psychiatric and medical conditions, such as anxiety disorders, other substance abuse, obsessive compulsive disorder, impulse control disorders, eating disorders, personality disorders, cardiovascular and respiratory disorders, and sleep apnea. The presence of alcohol and other SUDs increases the risk for chronic infectious diseases as well such as hepatitis B and C, HIV infection as well as increased risk for trauma, injury, and suicide (12,21–23). The presence of multiple comorbid psychiatric disorders not only confounds, and aggravates the presenting symptoms in patients with bipolar disorder, but may also increase their vulnerability to developing SUDs as well (24–27).

Anxiety symptoms, recently considered as cross-cutting symptoms in bipolar disorder in by DSM-5 and are assessed dimensionally (5), are reported to be associated with greater likelihood of suicide attempts, decreased response to treatment, and poor prognosis in bipolar disorder (21,28–31). Another key issue of comorbidity in bipolar disorder and SUD is the somewhat overlapping early age of onset for both disorders, which occur in during the crucial developmental period of teenage years to early adulthood (32). Teenagers with bipolar disorder are five times more likely to develop SUDs (17).

Management of bipolar disorder with comorbid SUD

A number of challenges are present throughout the process of care for these patients. These include identification and diagnosis of bipolar disorder in the context of SUDs, treatment engagement, selection of effective pharmacotherapy, and psychotherapy, addressing the appropriate phase of treatment from detoxification and control of the acute bipolar episode to the maintenance and recovery phase of care. These challenges and complexities presented by clinical comorbidities called into questions single-disease focused models of care and highlighted the need for integrated care.

Diagnosis of bipolar disorder in the context of substance abuse

Establishing a diagnosis of bipolar disorder by itself is challenging, and the literature reports a period of 10-year lag from the first appearance of symptoms to establishing a bipolar diagnosis. This lag is thought to be due in large part to the difficulty in ascertaining a

history of manic symptoms and that most patients seek help during a depressive episode (33). The presence of comorbid substance abuse exacerbates these difficulties as they can produce symptoms that mimic, overlap, obscure, or exacerbate the manifestation of the bipolar disorder. The potential impact of specific types of drugs of abuse on bipolar symptoms is reviewed elsewhere (12). The diagnostic ascertainment is further complicated by the high rates of mixed and rapid cycling subtypes among bipolar disorder with comorbid substance abuse. Both overdiagnosis as well as underdiagnosis of bipolar disorder have been reported in treatment-seeking patients with SUDs (34,35).

The use of structured instruments and screening tools may aid in improving diagnostic accuracy. Commonly used rating scales such as the Young Mania Rating Scale (36) or the Bech–Rafaelsen Mania Scale (37) have been regularly utilized in studies of this comorbid condition. Furthermore, the symptom checklist (SCL-90) (38) had shown high sensitivity and moderate specificity for mood disorders in patients with substance abuse. For a broad initial screening for manic and depressive symptoms, the Mood Disorder Questionnaire (39) may be helpful. Objective and structured diagnostic interviews (40,41) are helpful in confirming the categorical diagnosis consistent with bipolar disorder. Screening for alcohol and other substance of abuse can also be significantly facilitated by the use of screening instruments such as the Alcohol Use Disorders Identification Test (42) and the Drug Abuse Screening Test (43).

General treatment considerations

Several general management considerations for these patients with SUDs may impact on treatment adherence and course. Negative attitudinal issues and stigma toward patients with SUDs and psychiatric disorders, while improved, are still present at multiple levels (involving health-care providers, and sometimes the family, and the patient) and impact the care for these patients. Resistance to taking medications and to receiving treatment may be expressed by patients and/or families, and certain self-help groups discouraging the use of medications labeled as "mind altering." Moreover, suboptimal treatment adherence represents significant impediment to receiving adequate care in this population which may lead to high levels of residual symptoms. The presence of residual symptoms has been clearly related to frequent relapse to a full mood episode (44).

Furthermore, severe and chronic alcohol and/or other substance abuse may require medical treatment for the withdrawal syndrome, most frequently alcohol and opioid withdrawal, and less frequently benzodiazepine withdrawal. Although severe depression due to stimulants withdrawal may require inpatient observation for suicidal risk given the high rate of reported suicidal symptoms during cocaine withdrawal (45), limited evidence base is available on the optimal management of psychoactive substance withdrawal in bipolar disorder or other severe psychopathology. In addition to preventing withdrawal complications and alleviating the symptoms and distress of withdrawal, an important goal is also to introduce the patient to the long-term goal of initiating and maintaining sobriety as this period is viewed as a "window of opportunity" to introduce the concept of sobriety and recovery. The preferred treatment model for the management of withdrawal states is the use of objective rating scales to assess the presence of withdrawal symptoms and to use symptom-triggered medication dosing. For the alcohol withdrawal syndrome, the symptom-triggered approach is guided by the use of rating scale such as the Clinical Institute Withdrawal Assessment-revised (46). The use of such model was found very useful in alleviating withdrawal symptoms and minimizing withdrawal complications in among inpatients with mood and alcohol use disorders utilizing the diazepam loading dose (47). Symptom-triggered treatment reduces the likelihood of either under- or overuse of medication when compared to the standard medical detoxification methods (48). The use of long-acting benzodiazepines may offer an advantage over shorter acting medications because of the self-tapering properties of these medications. For opioid withdrawal, similar, symptom-triggered approach is employed utilizing the Short Opiate Withdrawal Scale (49).

Model of care for comorbid disorders

The need for integrated care has recently been emphasized as an important paradigm shift to adequately address the care for chronic and complex conditions such as the "Medical Care Home" (50) and the "Person-centered Integrative Diagnosis" (51–53) with refocusing of care from diseases-based to patient-centered care. Both bipolar disorder and SUDs have early age of onset during the developmental formative years (middle-to-late adolescence) and have a chronic and intertwining course. An integrated model of care will address both bipolar and addictive disorders, along with other associated conditions in the same setting and by the same care-provider team. A primary advantage of the integrated care approach is its attention, not only to the manifestation of the individual disorder but also to the dynamic and reciprocally deleterious

interactions between the comorbid conditions. Evidence from psychotherapy studies for this comorbidity, although limited, indicate that a therapy that integrates the attention to both disorders is more effective at decreasing alcohol or substance abuse compared to an intervention that only addresses the addictive disorder (54–56).

Furthermore, both disorders have similar phases of treatments which range from acute stabilization to maintenance treatment. Relapse prevention in both illnesses benefit from concerted efforts at recovery and health restoration. While there has been increased access to integrated care programs over the past decade for substance abuse and mental illness, there is still a significant unmet treatment need in terms of effective interventions specifically tailored to this population.

Targeted intervention strategies

Effective interventions that specifically target bipolar disorder with comorbid SUDs are still an area of unmet treatment needs. Trials for bipolar disorder and those for alcoholism have systematically excluded comorbid conditions. Integrated psychotherapeutic interventions and pharmacotherapies specifically addressing the comorbid condition are the two key treatment modalities that have been tested.

Integrated psychotherapies

While a number of empirically tested effective psychotherapies are available for non-comorbid bipolar disorder and SUDs, there is limited number of psychotherapies specifically tailored for patients with bipolar disorder with comorbid SUDs. Psychotherapy is essential for enhancing treatment alliance and adherence to treatment and medication, in addition to helping patients develop coping skills to optimize disease management, relapse prevention, and the recovery process.

Group therapy

Integrated group therapy (IGT) (54,55) was developed for the treatment of comorbid bipolar and addictive disorder. IGT-essential features are the integration of therapeutic interventions addressing both the bipolar disorder with drug counseling principles of SUDs. Two randomized controlled trials compared IGT to standard group drug counseling, one with community-based adaptation. IGT significantly decreased days of alcohol and substance use during treatment and follow-up compared to standard group drug counseling. This study highlights the importance of an integrated focus on both disorders to improve the alcohol and substance abuse outcome.

Individual counseling

Early recovery adherence therapy (ERAT) (57) specifically designed to help patients with bipolar disorder and comorbid SUD. This integrated individual therapy was designed to address bipolar disorder with comorbid alcoholism and other addictions during the early phases of recovery from an acute episode. It integrated principles and techniques from motivational enhancement therapy, relapse prevention, and from educational and disease management approaches of bipolar disorder and of alcoholism. ERAT had shown significant advantage over 12-step facilitation therapy on decreasing alcohol use and depressive symptoms in a randomized pilot study of patients with bipolar disorder and comorbid alcoholism.

Pharmacotherapy

Pharmacotherapy of comorbid conditions present additional challenges. An ideal medication for this population would be effective for both bipolar disorder symptoms and in reducing for of the substance abused, be well tolerated, free of problematic interactions with the substance abused or concomitant medications, and be without addiction potential. However, evidence-based effective pharmacotherapy for bipolar disorder with comorbid alcohol and other SUD's is still limited (58,59). Studies evaluating the efficacy of treatment for bipolar disorder, including pivotal studies seeking indications for the various bipolar states, systematically exclude people with substance abuse which leaves out a significant subgroup of patients with bipolar disorder with unmet treatment needs, as it is unclear how effective these treatments are for them. There has been only one large-scale, multisite study conducted for this population. All other randomized, placebo-controlled trials have been conducted at one site, and most of these studies had suffered from low recruitment retention rates. We present a narrative review of published randomized controlled trials for bipolar disorder with comorbid SUDs.

Two predominant paradigms have been utilized in selecting promising agents for this population. Most frequently, a single medication used in bipolar disorder has been tested to see if it affects not only the mood state at hand but also the addictive disorders. These trials highlighted the pharmacological effect of the chosen medication that may be useful for addictive disorders. These trials included the mood stabilizer lithium carbonate, the anticonvulsants sodium valproate and

lamotrigine, and the atypical antipsychotic, quetiapine. The second paradigm relied on testing medication approved for alcoholism or medications with promising pharmacological profile in helping with addictive disorders as an add-on to ongoing mood stabilizers. These included trials with add-on naltrexone, acamprosate, and the cognitive enhancer citicoline.

Mood stabilizers

Lithium carbonate, among the earliest medications in modern psychiatry and still among the most effective mood stabilizers, was tested in a small ($N = 21$), 6-week, double-blind placebo-controlled pilot study of adolescents with bipolar I or II disorders. The sample was heterogeneous but mainly abused alcohol and marijuana and the age of onset of bipolar disorder preceded that of SUD by almost 6 years. Patients who were treated with lithium carbonate monotherapy had significantly more negative urine drug screen (mostly marijuana) and improved scores of the global clinical impression compared to those on placebo (60). Treatment responders had a therapeutic blood level of 0.9 mEq/L. It should be noted that untreated mood states is a risk factor for continuing substance abuse; thus, the treatment response may have been mainly to stabilize the mood states and not for independent effects of lithium carbonate such as the substance abuse.

Anticonvulsants

Anticonvulsants, such as sodium valproate and carbamazepine, have been found to be helpful in alcohol withdrawal, as well as in alcohol and cocaine abuse without comorbid disorders (61,62). The GABAergic and glutamatergic activities as well as the dopaminergic modulation of some anticonvulsants have been highlighted as a putative mechanism underlying their utility in the treatment of substance abuse. Also, open-label pilot studies have found sodium valproate (63–65) useful for decreasing alcohol abuse, and lamotrigine (66) was reported to be helpful in the treatment of cocaine abuse in bipolar disorder. Both sodium valproate and lamotrigine are well-tolerated medications and thus are of particular interest in the treatment of bipolar disorder with comorbid SUDs (67,68).

Sodium valproate was tested in a 6-month, double-blind, placebo-controlled trial of divalproex sodium added to lithium carbonate ($N = 59$) in patients with DSM-IV bipolar I disorder and alcohol dependence (69). Patients were in active mood episode [either manic (25%), mixed (50%), or depressive (25%) states] and had substantial alcohol abuse (60 weekly standard drinks for the depressive subtypes, compared to 90 of the mixed states and over 110 for the manic subtype). Patients randomized to divalproex sodium added to lithium carbonate reported significantly less proportion of heavy drinking days (HDDs) as well as fewer standard alcohol drinks per heavy drinking and had longer period to sustained heavy drinking compared to those on placebo added to lithium carbonate. Patients on divalproex reported an average of five drinks per HDD (HDD is defined as four or more standardized drinks [SD] for females or five or more drinks for males) while patients assigned to placebo reported drinking on the average twice as much (10 SD/HDD). Treatment was well tolerated and this on divalproex sodium had significantly lower gamma glutamyl transpeptidase (GGT) compared to placebo. GGT is a sensitive marker to alcohol use which provided an indirect objective validation of reported decrease in consumption among this group. Valproate blood levels (maintained within a range between 50 and 100 μg/mL) were inversely correlated with decrease in alcohol use. This was also the only 6-month trial conducted to date for this population.

Lamotrigine. Brown and colleagues (70) tested in randomized, double-blind, placebo-controlled 10-week trial of a sample of 120 patients with bipolar disorder, who were in the depressed or mixed phase, and comorbid cocaine dependence. Dose titration of lamotrigine (from 25 to 200 mg, although increase to 400 mg was allowed based on clinical response) was accomplished over a period of 5 weeks. The primary outcome measure was urine drug screens positive for cocaine. Patients randomized to lamotrigine did not differ from placebo on primary outcome (urine screen) or on self-reported number of cocaine use days. Those on lamotrigine, however, had significantly less self-reported amount of money spent on cocaine. Changes in depressive symptoms strongly correlated with changes in self-reported cocaine use. This study highlights the link between depressive symptoms and cocaine abuse, which may be secondary to the use itself and it may reflect the worsening of bipolar depression in the presence of cocaine use. Assuming money spent on cocaine may indirectly reflect the quantity of cocaine obtained, lamotrigine may have decreased the quantity but not the frequency of use. It would have been instructive to know whether there was a decrease in money spent on cocaine correlated with the reported consequence of cocaine use or with change in overall functioning.

Topiramate. Sylvia and colleagues (71) recently published the results of a randomized, placebo-

controlled trial of topiramate compared to placebo in 12 patients with bipolar I and II disorders and comorbid alcohol dependence. Those who were on topiramate (n = 5) reported worse alcohol outcome and had higher dropout rate than those on the placebo group. The authors cautioned on drawing conclusions from the results of this study because of the small sample size as well as the high dropout rate reported.

The atypical antipsychotic quetiapine

Quetiapine, with its broad mechanism of action on several neurotransmitters and for its proven efficacy for both the depressive and the manic phases of bipolar disorder, represents an interesting choice for use in comorbid population (72). Also a pilot, open-label study reported promising results for quetiapine in comorbid bipolar disorder and alcoholism (73). Quetiapine has been the most tested medication for bipolar disorder with comorbid alcoholism. Three relatively large clinical trials tested the efficacy of quetiapine as an add-on medication in patients with bipolar disorder and alcoholism. Brown and colleague (74) conducted 12-week, randomized, placebo-controlled trial of add-on quetiapine (titrated up to 600 mg/day) in 102 outpatients with bipolar I and II disorders and alcohol dependence. Patients were mostly in the depressive phase (82%). Quetiapine was helpful in decreasing the depressive symptoms compared to placebo. Quetiapine, however, was not significantly better than placebo on alcohol use outcomes. **Quetiapine** was tested in a large (N = 362), multisite, randomized, placebo-controlled trial (not only up to 400 mg, but also allowed flexible dosing (300–800 mg/day) as an add-on medication (to either lithium or valproate) (75). Quetiapine did not have an advantage over placebo on alcohol use outcome including change in the proportion of HDD from baseline to week 12 (primary outcome) or secondary alcohol outcomes (time to the first consecutive 2 weeks of abstinence, changes from baseline to week 12 in the proportion of nondrinking days, mean number of SDs per day, and Clinical Global Impressions Severity of Illness score).

Quetiapine was tested in a third (76) randomized, placebo-controlled, 12-week trial of bipolar I or II disorders, who were in depressed or mixed mood state and current alcohol dependence. Ninety outpatients with high alcohol consumption were randomized to receive add-on sustained release quetiapine, titrated up to 600 mg/day. Quetiapine did not have an advantage over placebo in decreasing alcohol-related outcomes.

Medications used for alcohol use disorder

Disulfiram, naltrexone hydrochloride, oral formulation and naltrexone hydrochloride monthly intramuscular formulation, and acamprosate are currently approved in USA. Food and Drug Administration for the treatment of alcohol dependence and nalmefene, recently approved in Europe. There are two small trials that tested the utility of naltrexone and acamprosate for bipolar disorder with comorbid alcohol dependence.

Naltrexone hydrochloride is a pure opiate antagonist that presumably decreases alcohol use and relapse by decreasing the positive reinforcing effects of alcohol ingestion. Naltrexone was tested in pilot studies and in a small randomized controlled pilot trial and in a sample of veterans population which included bipolar disorder patients. Naltrexone (50 mg/day dose) was tested in a double-blind, placebo-controlled trial an addition of 50 patients (77,78). Patients randomized to naltrexone showed a trend toward advantage over placebo on decrease in drinking days and alcohol craving with generally medium effect sizes (77). Naltrexone also was reported to significantly decrease alcohol use in a small, open-label randomized study of naltrexone added to divalproex as compared to divalproex alone (79). Disulfiram-alone was compared to naltrexone-alone and to the combination of disulfiram and naltrexone in a large VA-based study, which included not only major psychiatric disorders, mainly major depression, but also included bipolar disorder and schizophrenia (80). Naltrexone or **disulfiram** used alone or in combination was tolerated by this population. While the combination of disulfiram and naltrexone was not superior to either medication alone, those who were on these medications had significantly more consecutive weeks of abstinence and less craving than those treated with placebo. Nalmefene is a newer opiate antagonist that is structurally similar to naltrexone but with potential advantage of not having dose-dependent liver toxicity (81). While nalmefene has not been tested in patients with bipolar disorder and comorbid alcoholism, it was found effective in reducing alcohol consumption when used on an as-needed bases as well (82).

Acamprosate presumably acts by alleviating the negative reinforcing effects of alcohol withdrawal and is classified as a modulator of glutamate neurotransmission. Acamrposate (1998 mg/day) was tested in an 8-week, randomized, double-blind, placebo-controlled trial in 33 patients with bipolar I or II disorder and concurrent alcohol dependence. Acamprosate was not better than placebo on alcohol outcomes (83). *Post-hoc*

analyses showed that acamprosate was better than placebo on clinical global impression in weeks 7 and 8.

Citicoline, a modulator of phospholipids metabolism and cholinergic systems, reported to improve cognition. Citicoline was tested in two studies by Brown and colleagues (84) for bipolar disorder and comorbid cocaine dependence. The first study was a 12-week, randomized, placebo-controlled, parallel-group, add-on, proof-of-concept trial in 44 outpatients with a bipolar disorder and cocaine dependence. Patients randomized to the citicoline group had significant advantage over placebo on less likely to have cocaine positive urine. They also had an advantage over placebo on significantly improving aspects of declarative memory (84).

Citicoline was tested in a recently published study by Brown and colleagues (85). Citicoline was tested in a randomized, placebo-controlled trial, 12-week trial of 130 participants with bipolar disorder and cocaine dependence. The results indicated a treatment group and a group-by-time effects showing an advantage of citicoline over placebo. The advantage was more pronounced early in treatment and tended to diminish over time.

A third study of **citicoline** by Brown and colleagues (86) evaluated the efficacy of citicoline in a sample of patients with bipolar disorder and methamphetamine dependence. The study included 60 adults with depression (either bipolar depression or major depressive disorder) and comorbid methamphetamine dependence. Patients were randomized to citicoline (2000 mg/day) or placebo for 12 weeks. Citicoline had a significant advantage over placebo on depressive symptoms. However, there was no difference on methamphetamine outcome or memory functions.

Conclusion

Bipolar disorder is highly likely to develop a SUD along with other comorbid disorders. The presence of an alcohol and SUD complicates the clinical presentation, treatment, and course of bipolar disorder and is associated with negative consequences, including worsen symptoms severity, increased suicide risk, and inpatient hospitalization in addition to increased medical morbidity and social problems. Clinical challenges include diagnostic ascertainment, suboptimal treatment adherence, and impediments to accessing adequate care. Integrated chronic disease treatment model that addresses both disorders is the preferred management approach with focus on achieving and maintaining sobriety, symptoms, and episode remission, along with enhancing recovery and health restoration. Few empirical studies have been conducted and treatment needs for this comorbid condition are still largely unmet. Group and individual integrated psychotherapies that address both disorders and their dynamic interactions appear more effective than interventions focusing on either disorder alone, although larger studies in diverse settings are still needed. Pharmacotherapy trials have focused on alcohol and cocaine/stimulant use disorders. It is important to note that there are no published trials to date addressing tobacco (87) or opioid use disorders (88) among this population. The mood stabilizer, anticonvulsant valproate sodium, and medications used for alcoholism, such as naltrexone, have also shown promise for this population and indicate the need for larger, multisite studies to establish their efficacy.

Disclosure statement

The authors report no relevant financial conflicts.

Notes on contributors

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