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Pharmacotherapy Options in Comorbid Bipolar Disorder and Alcohol-Substance Use Disorders

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ÖZET:

Bipolar bozukluk ve alkol-madde kullanım bozuklukları eştanısında farmakolojik tedavi seçenekleri

Epidemiyolojik çalışmalar, bipolar bozuklukta en sık eşlik eden Eksen I psikiyatrik hastalığın alkol-madde kullanım bozuklukları olduğunu bildirmektedir. Eşlik eden alkol-madde kullanım bozuklukları bipolar bozukluk seyrini kötüleştirmekle birlikte bu iki hastalık arasındaki ilişkinin altında yatan mekanizma halen açıklığa kavuşmamıştır. Yine de, bipolar bozukluk ve alkol-madde kullanım bozuklukları arasında gözlenen muhtemel ilişki, her iki hastalık grubunu kapsayan tedavi stratejileri geliştirilmesini sağlayan klinik uygulamaları desteklemektedir. Biz de bu derlemede, kısıtlı sayıdaki çalışmalara rağmen, bipolar bozukluğa eşlik eden alkol-madde kullanım bozukluklarının farmakolojik tedavisini gözden geçirmekteyiz. Alkol-madde kullanım bozukluğu eştanılı bipolar bozukluk her bir hastalık dönemi için tedavi seçenekleri kanıta dayalı birinci sıra ve uzman görüşü ikinci sıra olarak depresif dönem için ketiapin, lityum ve valproat; manik/karma dönem için valproat ve ketiapin; idame dönemi için ise valproat monoterapisi veya naltrekson/dilsülfiram şeklinde gruplandırılmıştır. Bipolar bozukluğa eşlik eden alkol-madde kullanım bozukluğu tedavisini geliştirmeye dönük uzunlamasına izlem çalışmalarına ihtiyaç vardır.

Anahtar sözcükler: bipolar bozukluk, alkol-madde kullanım bozuklukları, eştanı, tedavi, farmakoterapi

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ABSTRACT:

Pharmacotherapy options in comorbid bipolar disorder and alcohol-substance use disorders

Epidemiological studies have reported that alcohol-substance use disorders are the most common co-occuring axis I disorder among patients with bipolar disorders. Comorbidity of alcohol-substance use disorders mostly worsens the course of illness in bipolar patients and underlying mechanisms of the association between both disorders still remain unclear. However, the prospective links observed between bipolar disorders and alcohol-substance use disorders support clinical interventions that incorporate both disorders in developing treatment strategies. Here we review the pharmacological treatment choices for alcohol-substance use disorders accompanying bipolar disorders, despite a limited number of treatment studies. The first-line (evidence-based) and second-line (expert opinion) pharmacological agents of bipolar disorder with comorbid alcohol-substance use disorders are quetiapine, lithium or valproate for the depressive phase; valproate or quetiapine for the manic/mixed phase, and valproate monotherapy or a combination of valproate with naltrexone or disulfiram for maintenance. Future prospective studies are required for improvement of treatments in comorbid bipolar and alcohol-substance use disorders.

Keywords: bipolar disorders, alcohol-substance use disorders, comorbidity, treatment, pharmacotherapy

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INTRODUCTION

There is a growing body of literature addressing the comorbidity of substance use disorders (SUD) and bipolar spectrum disorders. The rate of SUD in bipolar disorders (BD) is higher than in the general population. Epidemiological studies have reported that SUD is the most common co-occuring Axis I disorder in patients with BD. In the National Comorbidity Survey (NCS), it was reported that the risk of alcohol dependence is 10-fold and psychoactive substance dependence is 8-fold higher for patients with BD compared with the general population (1-3). In the National Institute

of Mental Health (NIMH) Epidemiologic Catchment Area (ECA) study (3), life time prevalence of co-occurring SUD and BD was 60.7% and further analysis of ECA data showed that persons with BD had the highest lifetime prevalence of SUD, followed by persons with schizophrenia, panic disorder, and unipolar depression (4). Among subtypes of BD, the rate of lifetime alcohol use disorders (AUD) was higher for persons with bipolar I (BPI; 46%) comparing with bipolar II (BPII; 39%) (3).

Considering the high prevalence of SUD among bipolar patients, the impact of substance use on the course of BD becomes more important and it is a well-known fact that this comorbidty makes the clinical course of the illness more severe and worse (4). However, these patients are mostly treated for only one disorder either alcohol-substance or mood disorders. This perspective comes from the widespread clinical approach that treating the primary disorder is the best way to reach remission even though it often fails. The reason for this useless approach might be the limited amount of data and guidelines on the treatment of this specific group of patients. Currently, however, there are growing numbers of clinical studies and expert opinions for patients with comorbid BD and SUD.

In this review, we aimed to assess the current status of pharmacological treatment options for bipolar patients with alcohol-substance use and to evaluate this evidence to provide a useful paradigm for clinical practice.

Clinical Course of Comorbidity

Bipolar patients with SUD have been typically associated with a higher prevalence of other psychiatric and physical comorbidities (5-6). Compared to patients without SUD, bipolar patients with comorbid SUD have an earlier age of illness onset and psychosis in their first episode (4,5,7,8). Comorbid SUD negatively affects the course, treatment outcome, and prognosis of BD. Patients with comorbid BD and SUD experience faster onset and longer duration of mood episodes and also shorter duration of remission intervals between episodes (4,5). In particular, they have an increased frequency of depressive onset and higher numbers of depressive episodes with increased rates of suicidal attempts (9,10). Also, BD with SUD is associated with aggressivity, and impulsivity (11-14). Despite the longer duration of mood episodes, interestingly these patients are more likely to experience a switch from depression to mania/hypomania or a mixed state leading to a shortened cycle length between episodes and an increased frequency/total number of mood episodes (4-7,10). Thus, they experience frequent hospitalizations which are more likely to lead to increased health service use and costs (15). Consequently, all these factors result in prolonged recovery time and an increased burden of residual symptoms and it may be concluded that bipolar patients with SUD have a more severe subtype of illness (such as rapid cycling, mixed and dysphoric states) and treatment-resistant variants of BD (5-8). These patients have lower life satisfaction and poorer cognitive functioning (6,9). On the other hand psychosocially, they are less likely to be living with both biological parents, have a greater lifetime prevalence of physical-sexual abuse, a greater prevalence of pregnancy and abortion and a greater prevalence of forensic problems (4-8,10,15).

The precise nature of the association between SUD and BD still remains unclear and may reflect several different underlying mechanisms. The different patterns of association between mood disorders and substance use pathways have important implications for prevention and provide some missing information about underlying mechanisms. In terms of clinical implications, the prospective links observed between BD and SUD support clinical interventions that incorporate both disorders in developing treatment strategies (16). Despite the high prevalence of this comorbidity, there are only a few evidence-based treatment choices for both disorders. Using SUD comorbidity as an exclusion criterion for treatment studies might be one of the main reasons. Despite the limited number of treatment studies, we have summarized evidence-based treatment choices for comorbid BD and SUD below.

Pharmacological Treatment of BD and SUD Comorbidity

Treatment and management of comorbidity of BD and SUD includes different phases of illness such as acute, continuation and maintenance. The acute phase focuses on treatment engagement, wash out from drugs and/or alcohol, and stabilization of the bipolar episode. The continuation phase focuses on consolidation of response into stable remission and making personal and lifestyle changes to reinforce sobriety. The maintenance phase focuses on reducing the risk of relapses of both SUD and mood disorders (7). Therefore, several treatment strategies can be chosen for different phases of illness. There is a huge body of literature showing the efficacy of many pharmacological agents for the treatment of SUD or BD separately, whereas there is lack of knowledge about pharmacotherapy of comorbid BD and SUD which we will try explain.

Lithium: In two different double-blind placebo-controlled clinical trials evaluating the efficacy of lithium carbonate, it was not found to be effective in the treatment of patients with alcohol use disorder (AUD). In the first study, published by Fawcett et al. (17) it was found that lithium was not better than buspirone or placebo on decreasing alcohol use among 156 subjects with alcohol dependence. In the second study, similarly, Dorus et al. (18) reported that lithium was not better than placebo with respect to the number of patients achieving abstinence, number of drinking days, severity of alcoholism, and severity of depression among 457 detoxified male alcoholics. On the other hand, in an open label study, lithium showed a nonsignificant decrease in cocaine use among cocaine users with BD (19). Consistently, it was found in a 6-week randomized, double-blind, placebo-controlled study; among 25 adolescents with BD and secondary SUD (mostly alcohol and marijuana) that lithium was significantly superior to placebo in reducing substance use and improving functioning (20).

Also, lithium had a positive effect in treating alcohol dependence that is independent of the patient's motivation and the effect of lithium on depression (4). In APA guideline (21), lithium is recommended as a first line choice for bipolar depressive patients with substance use. There are no specific studies about treatment of bipolar

Table 1: Lithium trials among patients with alcohol-substance use disorders

Treatment choice	Author	Study design	Results
Lithium	Fawcett et al. (17)	Double-blind placebo- controlled copmarison of lithium, buspiron, placebo in subjects with alcohol dependence (n=156).	Lithium was not better than placebo or buspirone on decreasing alcohol use.
	Dorus et al. (18)	Double-blind placebo- controlled copmarison of lithium and placebo among detoxified male patients wtih alcohol dependence (n=457)	Lithium was not better than placebo in terms of the number of patients achieving abstinence, number of drinking days, severity of alcoholism, and severity of depression
	Nunes et al. (19)	Open label study of lithium among cocaine abuser bipolar patients (n=10).	Nonsignificant decrease on cocaine use
	Geller et al. (20)	6-week randomized, double-blind, placebo-controlled study among adolescents with BD and secondary SUD (mostly alcohol and marijuana).	Lithium was significantly superior to placebo in reducing substance use and improving functioning.
	Kemp et al.(22)	6-month, double-blind, parallel-group comparison of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar patients with comorbid substance abuse or dependence (n=31).	Combination of divalproex with lithium had no additional prophylactic benefit over lithium monotherapy.

depression in substance-abusing individuals. More recently, in a 6-month, double-blind, maintenance trial of lithium monotherapy comparing the combination of lithium and divalproex for rapid-cycling bipolar disorder and comorbid SUD, 149 patients were enrolled into the open-label acute stabilization phase and of these, 31 patients (21%) were randomly assigned to double-blind maintenance treatment (22). A small group of the patients (26%, n= 8) completed the study and the median time to recurrence of a new mood episode was found to be 15.9 weeks for lithium monotherapy group while it was 17.8 weeks for the combination group. This difference was not significant which means that addition of divalproex to lithium conferred no additional prophylactic benefit over lithium alone (22) (Table 1).

Anticonvulsants: The kindling model has been proposed for both BD and SUD. From this point of view, the anti-kindling anticonvulsants such as carbamazepine and divalproex, which are first line treatments in BD, would appear to be ideal treatments for SUD, particularly for alcohol withdrawal (4) (Table 2).

Valproate: Some evidence suggests that patients with these co-occurring disorders are more likely to respond to valproate or a combination of valproate plus lithium than to lithium alone (21). Furthermore, bipolar variants, such as rapid cycling, mixed, and dysphoric subtypes, frequently found among comorbid bipolar disorder and SUD, are resistant to treatment with lithium carbonate and valproate may be somewhat more efficacious (7). It is also hypothesized that valproate might

Table 2: Anticonvulsant trials in comorbid BD and SUD

Treatment choice	Author	Study design	Results
Valproate	Brady et al. (25)	Open-label, nonblinded 16 week study among bipolar patients with comorbid substance dependence (five alcohol, three polysubstance abuse, one cocaine). (n=9)	Significant improvement in symptoms of depression and mania and a significant decrease in the number of days and amount of drug use after valproate use.
	Salloum et al. (26)	24-week, randomized, double-blind, placebo-controlled study in 59 subjects with BD and alcohol dependence	Divalproex was significantly superior to placebo in reducing the proportion of heavy drinking days and time to relapse to sustained heavy drinking is prolonged
Carbamazepine	Malcolm et al. (28)	Double-blind, randomized controlled comparison of lorazepam and carbamazepine among patients with alcohol withdrawal. (n=136)	Lorazepam and carbamazepine were equivalent in regard to withdrawal symptoms. Carbamazepine was superior to lorazepam in preventing rebound withdrawal symptoms and reducing post-treatment drinking, especially for the patients with a history of multiple treated withdrawals.
	Brady et al. (29)	12-week, double-blind, placebo-controlled study in cocaine dependent patients with (n=57) and without (n=82) affective disorders.	CBZ-treated affective group had a trend toward fewer cocaine-positive tests and a significantly longer time to first cocaine use. CBZ treatment did not have any impact on cocaine use in individuals without affective disorders.
Lamotrigine	Brown et al. (37)	12 week, open-label study in cocaine abusing patients with BD. (n=30)	Lamotrigine monotherapy or in addition to usual treatment was associated with significant improvement in mood and drug cravings but not cocaine use.
	Brown et al. (38)	36 week open-label study in cocaine abusing patients with BD. (n=62). Extension of the Brown et al. (38) stduy sample.	Lamotrigine treatment (mono or combination) was associated with significant improvements in mood, drug craving and drug use.

reduce drug cravings and promote abstinence with its pharmacological properties (23). On the other hand, trials have noted that treatment adherence with valproate might be better than lithium in patients with SUD and BD. Because, patients are rarely warned not to drink alcohol while taking lithium, this may affect their compliance (24). In addition, the difficulty of patients with comorbid BD and SUD in achieving stable lithium blood levels may play a role in the relative lack of efficacy with lithium (21).

In a non-blinded, open-label study conducted by Brady et al. (25), nine bipolar I patients with SUD were given valproate and it was found that patients had significant improvement in symptoms of depression and mania and a significant decrease in the number of days and amount of drugs used during a 16-week follow-up period. In a 24-week, randomized, double-blind, placebo-controlled study in 59 subjects with BD and alcohol dependence, Salloum et al. (26) found that divalproex was significantly superior to placebo in reducing the proportion of heavy drinking days. Furthermore, the time to relapse in sustained heavy drinking was prolonged with valproate, compared with the placebo group.

Carbamazepine: One of the most commonly used anticonvulsants in the treatment of both SUD and BD is carbamazepine as an anticonvulsant/anti-kindling drug like valproate with the same potential usefulness. In their review, Williams and McBride (27) concluded that carbamazepine might be a first-line alternative to benzodiazepines for alcohol withdrawal symptoms. Consistent with this observation, in a double-blind, randomized controlled trial, it has been reported that lorazepam and carbamazepine were equivalent in regard to withdrawal symptomatology (28). However, in patients with two or more previous detoxifications, carbamazepine was superior to lorazepam in preventing rebound withdrawal symptoms and reducing post-treatment drinking (28). On the other hand, Brady et al. (29) studied the efficacy of carbamazepine in patients with BD and cocaine dependence. In this double-blind, placebo-controlled study including 139 cocaine-dependent patients (57 with and 82 without affective disorders), carbamazepine was associated with fewer positive urine drug screens and a longer time to cocaine use, but carbamazepine had no impact on cocaine use in subjects with mood disorders (29).

Consistently, in a meta-analysis of five studies among cocaine dependent patients, it was reported that there was no difference between carbamazepine and placebo in terms of urine testing for cocaine use. Thus, evidence does not support the use of carbamazepine in the treatment of cocaine dependence (24). However, carbamazepine (600–800 mg/day for the first 48 hours; then tapered by 200 mg/day) has been demonstrated to be effective in preventing withdrawal-related seizures, although its tendency to lower white blood cell counts in some patients may pose an added risk of infection (21). Additionally, carbamazepine has a complicated pharmacokinetics profile and it may require numerous dosage adjustments and monitoring to achieve a steady state because it induces its own metabolism. This further increases the complexity of the treatment regimen with negative impact on medication compliance (7).

Oxcarbazepine: Despite the fact that oxcarbazepine has not been studied among patients with comorbid BD and SUD, it may be useful as an alternative to carbamazepine as shown in the study by Schik et al. among patients with SUD only (30). In a pilot study, Croissant et al. (31) showed that oxcarbazepine is as effective as acamprosate among alcohol-dependent patients for relapse prevention. Similarly, a high dosage of oxcarbazepine (1500-1800mg/day) was superior to naltrexone (50mg/day) and a low dosage of oxcarbazepine (600-900mg/day) in terms of relapse prevention among 84 detoxified alcohol dependent patients (32). However, in a double-blind, randomized, placebo-controlled multicenter pilot study, Koethe et al. (33) could not find any difference between oxcarbazepine versus placebo in terms of withdrawal symptoms and craving for alcohol.

Lamotrigine: Lamotrigine is particularly used for preventing depressive relapses and is approved by the FDA for maintenance treatment in bipolar patients (34). Lamotrigine is also effective for the treatment of rapid-cycling bipolar patients (35). A case report suggests that lamotrigine is safe and effective in rapid-cycling refractory BD with comorbid SUD (36). In a small open-label study in cocaine abusing patients with BD, Brown et al. (37) reported that lamotrigine, alone or in addition to usual pharmacotherapy, was associated with significant improvement in mood and drug cravings but not cocaine use. Later on, in a replication sample among patients with BD and cocaine dependence, Brown et al. (38) found that lamotrigine was associated with significant improvements in mood, drug craving and drug use. There are also case reports about the use of lamotrigine for the treatment of naloxone-precipitated opiate withdrawal (39) and inhalant dependence (40). But clinicians should consider that lamotrigine should be used cautiously in individuals with comorbid BD and SUD. Because active substance users may be unreliable in reporting rashes, gradual titration of lamotrigine is needed and may be problematic in individuals, who may be predisposed to taking excessive medication doses, and drug-drug interactions may alter lamotrigine levels and increase the risk of rash (21).

Other anticonvulsants: Newer anticonvulsants such as gabapentin and topiramate show potential as treatments for SUD (41), however these medications are not effective for treatment of BD. There are just case reports and limited numbers of small sample sized open label studies with gabapentin or topiramate among patients with SUD and BD comorbidity (42).

Second generation antipsychotics (SGAs): In recent years, most SGAs have been approved for the treatment of BD, particularly for the manic phase of the illness. Although there is enough data

Table 3: Trials with SGA in comorbid BD and SUD

Treatment choice	Author	Study design	Results
Quetiapine	Brown et al. (46)	12 week, double-blind, randomized add on trial of quetiapine(600mg/d) among BD patients with alcohol dependence. (n=115)	Quetiapine was found to be associated with significant improvement in depressive symptoms, but not alcohol use.
	Stedman et al. (47)	12 week, double-blind, placebo-controlled study with quetiapine add on lithium or divalproex in bipolar I patients with comorbid alcohol dependence. (n=362)	No significant difference between placebo and quetiapine in terms of alcohol and mood measures.
	Brown et al. (48)	12 week, open-label, add-on quetiapine treatment in BD patients with cocaine dependence. (n=17)	Significant improvement in mood and craving scores. No difference in the amount of money spent for the substance used, the frequency of the substance use, and the frequency of positive urine test results.
	Nejtek et al. (49)	20 week, randomized, double-blind comparison of quetiapine and risperidone among outpatients with substance-induced mood disorders. (n=124)	Both quetiapine and risperidone were associated with improvement in manic, mixed, and depressive symptoms and reduced drug cravings.
	Martinotti et al. (50)	16 week, open label study of quetiapine among detoxified alcohol dependent patients with comorbid diagnosis of BD, chizoaffective disorder, and borderlines personality disorder. (n=28)	Significant decrease in alcohol consumption, craving for alcohol, and psychiatric symptoms intensity.
Aripiprazol	Brown et al. (56)	12 week, open-label study, switching outpatients with bipolar or schizoaffective disorders and substance abuse from their current antipsychotic to aripiprazole. (n=20)	Significant improvement in symptom scores and significant decrease among patients with alcohol/cocaine dependence.

for schizophrenia (43), evidence for the treatment of comorbid BD and SUD with SGAs is still limited (see Table 3). SGAs owe their efficacy to dopaminergic antagonism in the reward pathway in mesocorticolimbic neurons (44).

Quetiapine: Quetiapine was reported to reduce substance use and craving due to its low affinity for dopamine receptors and its weak attenuation of central reward functions (45). There are only two double-blind, randomized add on trials of quetiapine among BD patients with alcohol dependence. In the first study, quetiapine was added to the treatment as usual of 115 BD patients (82% depressive) and titrated to a 600mg/d dose. After a 12 week follow-up period, quetiapine was found to be associated with significant improvement in depressive symptoms, but not alcohol use (46). However, in the second study, Stedman and colleagues could not replicate these findings and reported that there was no significant difference between placebo and quetiapine in

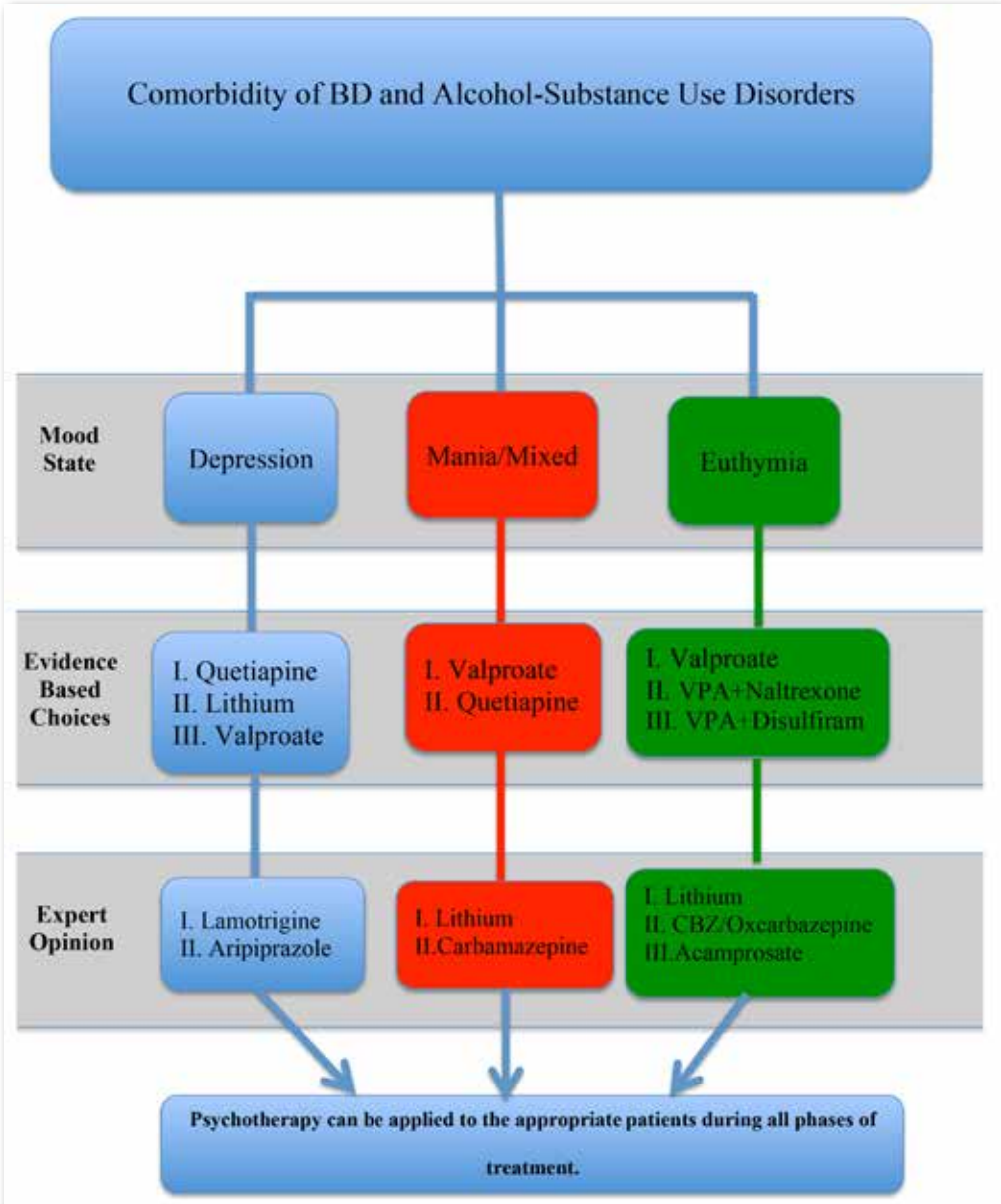

Figure 1: Algorithm for the treatment of comorbid BD and Alcohol-Substance Use Disorders

terms of alcohol and mood measures (47). These contradictory findings may due to study design and sample selection criteria. On the other hand, in an open label add on study, Brown et al. (48) reported that quetiapine alleviated mood symptoms and decreased cocaine craving among patients with comorbid BD and SUD. Interestingly, there was no difference in the amount of money spent for the substance used, the frequency of substance use, and the frequency of positive urine test results (48). In a randomized double-blind study, Nejtek et al. (49) compared the efficacy and tolerability of quetiapine and risperidone in the treatment of mood symptoms, drug cravings, and drug use in outpatients with comorbid BD and cocaine or methamphetamine dependence. They found that both quetiapine (n=42) and risperidone (n=38) significantly improved manic and depressive symptoms and reduced drug cravings. Quetiapine and risperidone were similar in their effects on mood symptoms, drug craving, or drug use (49). In another study, Martinotti et al. (50) evaluated the effectiveness of quetiapine among alcohol dependent patients with comorbid diagnoses of bipolar I, bipolar II, schizoaffective disorder, and borderline personality disorder. Patients were given a daily quetiapine dose of 300-800 mg for 16 weeks following detoxification treatment and it was found that quetiapine decreased the psychiatric symptoms that accompanied alcohol consumption and craving (50). Interestingly, there are also case reports of quetiapine abuse and dependence, in particular among prisoners and patients diagnosed with substance abuse (44,51). Thus clinicians should consider abuse potential of quetiapine.

Clozapine: Another SGA, clozapine with a unique receptor profile, appears to be associated with reduction in some patients with schizophrenia or schizoaffective disorders (52,53), but there is no evidence for the treatment of comorbid BD and SUD. In a recent report by Zhornitsky et al. (54), 43 studies were identified, including 23 studies in patients with comorbid SUD and psychosis and 20 studies in patients with SUD but without comorbid psychosis. In the comorbid SUD and psychosis group, it was found that SGA, particularly clozapine, might decrease substance use (mostly cannabis).

Aripiprazole: Aripiprazole is a partial and selective agonist of dopamine D2 receptors and has been approved for the treatment of the manic and maintenance phase of BD (55). Despite some evidence with aripiprazole for the treatment of SUD only, there is only one study evaluating the efficacy of it for comorbid BD and SUD (56). Twenty patients suffering an acute mood episode (11 depressive, 6 mixed and 4 manic) with a co-occurring SUD were included the study and followed for 12 weeks; all patients were switched from their previous treatment to aripiprazole. There was significant improvement in baseline scores at the end of the trial and patients with alcohol/cocaine dependence had a significant decrease in craving (56). Additionally, it was indicated that aripiprazole worked well in a patient with comorbid BD type II and polysubstance use during a six month follow up in a case report from France (57).

In light of this limited evidence regarding SGAs, clinicians should assess patient preferences and vulnerabilities regarding side effects, interactions with abused substances, and other safety considerations while choosing an antipsychotic medication (21).

Combination treatment with drugs approved for SUD: A combination strategy might be helpful for comorbid diagnosis of BD and SUD by augmenting the mood stabilizers with a medication aimed at maintaining abstinence such as naltrexone hydrochloride for alcohol dependence (7). Supporting this approach, in a randomized, open-label, pilot study, the combined pharmacotherapy of valproate + naltrexone was compared to valproate alone over an 8-week period. The combination of valproate plus naltrexone had a better outcome on avoiding relapse in alcohol use, on improvement of alcohol craving, and in mood symptoms (4). In a 12-week

randomized clinical trial, Petrakis et al. (58) compared the effectiveness of disulfiram and naltrexone between alcoholic patients with and without psychotic spectrum disorders. Within the group of patients with psychotic spectrum disorders, 48 (73%) had bipolar disorder. In each case, subjects with psychotic spectrum disorders that were treated with active medication (disulfiram or naltrexone) had significantly better outcomes, more days of abstinence and fewer total heavy drinking days when compared with subjects on placebo. On the other hand, a 12 week randomized double blind placebo controlled study by Brown and colleagues evaluated the impact of naltrexone 50mg/d add-on treatment among BP patients with active alcohol use (59). Although the degree of alcohol use numerically decreased in the naltrexone group, there was no significant difference from placebo in terms of drinking days and mood symptoms (59). Authors reported that larger sample size follow-up studies in this special group of patients would be helpful considering the trend toward reduction in alcohol use.

Additionally, acamprosate is a widely utilized, efficacious FDA approved treatment for relapse prevention in alcohol dependent patients (60). Considering the role of glutamatergic NMDA receptors in SUD and receptor profiles of two effective antipsychotics (clozapine, asenapine) for bipolar disorder (61-63), it is reasonable to speculate that acamprosate may provide a better and safer approach for the treatment of BD and SUD comorbidity. However, in an 8 week, randomized, double blind, parallel group placebo controlled study, Tolliver et al. could not show any improvement in drinking outcomes among comorbid BD and AUD patients (64). Considering the limited number of approved medicines in BD and SUD and the fact that acamprosate is well tolerated and safe, it could be a choice for some of patients experiencing severe cravings.

Psychotherapy

Beside these pharmacological treatment choices, psychotherapy must be kept in mind for the treatment of comorbid BD and SUD. Integrated psychosocial treatments for BD and SUD have been developed and demonstrated to be effective and group therapy–based treatment integrated cognitive-behavioral approaches are effective in treating both disorders. This approach includes educational, motivational, and coping strategies to enhance medication adherence and self-efficacy with cues and triggers for drug use (21).

CONCLUSION

Limited data indicates that pharmacotherapy for managing mood symptoms may be effective for the treatment of SUD, although findings are not consistent in all studies (65). There are shared treatment choices for both SUD and BD such as anticonvulsants. Some clinical evidence indicates that valproate is effective and seems to be superior to lithium for the treatment of comorbid SUD and BD; however, there is a lack of evidence with other mood stabilizer agents. There is an emerging body of literature with SGAs, particularly with quetiapine. Psychotherapeutic interventions, particularly motivational interview techniques, show promise. Further investigations and developments of concurrent BD and SUD should provide stronger evidence for clinicians to manage the treatment of this difficult comorbidity.

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