

Treatment of Comorbid Psychiatric Disorders with Bipolar Disorder

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ABSTRACT

Life time psychiatric comorbidities of bipolar disorders are highly prevalent. Anxiety disorders, alcohol-substance use disorders, obsessive-compulsive disorder and attention deficit and hyperactivity disorder are the most common comorbid psychiatric conditions in bipolar disorders. Psychiatric comorbidity of bipolar disorders is strongly associated with poor treatment response, higher recurrence of mood episodes, suicide attempts, rapid-cycling, worse general functioning and quality of life. Therefore, considering the huge impact of comorbidity on the bipolar disorder illness course, treatment is usually challenging. The primary aim of the treatment in psychiatric comorbidity of bipolar disorder should be mood stabilization and prevention of mood episodes. Then, first line treatment options recommended for the specific psychiatric disorders might be preferred for the treatment of bipolar disorder

comorbidity. With this rationale, quetiapine can be listed as a first line treatment for anxiety disorders comorbidity in bipolar disorders while serotonergic antidepressants and olanzapine are recommended as second line options. For the treatment of alcohol-substance use disorders comorbidity, first line mood stabilizers such as valproate and lithium and new generation antipsychotic quetiapine seem to be the leading options. Serotonergic antidepressants for obsessive-compulsive disorder and stimulants for the attention-deficit hyperactivity disorders are the key treatment choices. However, both treatment agents might cause to manic switch and mood destabilization. Thus, clinicians should be aware of these complications when prescribing in bipolar disorders comorbidity.

Keywords: Bipolar disorders, psychiatric comorbidity, treatment

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INTRODUCTION

Bipolar disorder (BD) is a chronic mood disorder characterized with recurrent mood episodes and may cause prominent disability if it is not treated sufficiently (1). BD is a systemic disease which may seriously influence the quality of life, even though remission between recurrent mood episodes can be seen in the course of illness (2). The fact that multi-systemic character of BD makes comorbidity a rule rather than an exception. Consistently, it is reported that lifetime comorbidity rates of psychiatric disorders or other medical conditions in BD are around 90% in the national and international literature (3, 4). Furthermore, it is indicated that about half of the patients with BD diagnosis is treated for at least three comorbidities (5).

Patients with BD diagnosis accompanied by other psychiatric disorders have an earlier onset of illness and it is associated with more frequent recurrence of mood episodes (3). Similarly, patients with recurrent episodes have higher rates of comorbidity comparing with the patients with the first manic episode (6). Additionally, mixed features in mood episodes and number of suicide attempts are higher in BD with comorbidity (7, 8). When high prevalence rates and negative effects on the course of illness are taken into consideration in bipolar patients with comorbidity, it will not be difficult to predict that treatment response will be worse compared to those without comorbidity (6).

The most common comorbid psychiatric disorders in patients with the diagnosis of BD are anxiety disorders, alcohol-substance use disorders (ASUD), obsessive-compulsive disorder(OCD), Attention

Deficit Hyperactivity Disorder(ADHD), personality disorders and eating disorders (6). The first four common comorbid disorders will be reviewed in this article since it would be difficult to provide comprehensive information about the diagnosis and treatment of all these comorbid psychiatric disorders.

TREATMENT FOR COMORBID ANXIETY DISORDERS AND BIPOLAR DISORDERS

The lifetime prevalence rates of anxiety disorder comorbidity in BD reach almost 90%, when panic disorder, social anxiety disorder and generalized anxiety disorder are considered as in the diagnostic group of anxiety disorders (9). It is known that depressive episode is more severe and substance use rate is higher, treatment response is worse and number of suicide attempts are higher when anxiety disorders are accompanying in patients with the diagnosis of BD (10). Despite it is thought that anxiety symptoms are more common in depressive episodes of bipolar patients, it is also common in euthymic phase. The rate of any anxiety disorder in euthymic bipolar patients is reported to vary between 7-50% (11, 12). As a result of the meta-analysis of all these epidemiological studies, it was found that 34.7% of euthymic patients with BD had at least one anxiety disorder and 4.6-fold increased risk of any anxiety disorders (10). When all diagnoses under the branch of anxiety disorders are reviewed, it was reported that the rate of generalized anxiety disorder (%11.6) was the highest (10). In another meta-analysis it was indicated that life time comorbidity of any anxiety disorder was 40.5% and panic disorder (18.1%)

was the most common accompanying anxiety disorder to the BD (9). The high comorbidity rates of BD and anxiety disorders is thought to be the consequence of the course of illness in BD facilitating the development of anxiety disorders associated with stressful life style and negative life events (13). On the other hand, it could be concluded that etiological pathways are shared considering the high rate of anxiety disorders before the BD diagnosis and higher prevalence of anxiety disorders in the family members of BD patients than general population (14).

The high comorbidity rates of life time anxiety disorders in patients with BD diagnosis and its negative impact on the clinical course of illness increase the importance of treatment. Antidepressants which are first-line treatment options in anxiety disorders should be carefully prescribed due to the risk of manic switch and rapid-cycling in BD. In the presence of anxiety disorder comorbidity in BD, it should be better to consider the treatment in two headings as mania-depression episodes and euthymia. Nevertheless, new generation antipsychotics (NGA) that are mainly approved for treatment of mania or depression are preferred for the treatment of mood episodes with anxiety symptoms. Although antidepressant can be considered in anxiety symptoms accompanying the depressive episode of BD, inconsistent results about their effectiveness in bipolar depression may limit their use. On the other hand, quetiapine comes into prominent due to its effectiveness in both depressive and anxiety symptoms of bipolar patients (15).

In the presence of anxiety disorder during the euthymic phase of bipolar disorder, the priority in the treatment should be the continuation of euthymia. At this point, lacking number of randomized controlled studies makes it difficult to offer clear recommendations for the treatment. In a 12-week single-blind pilot study; adding olanzapine (mean dose 7.7 mg/d) or lamotrigine (mean dose 96.7 mg/d) to the treatment of patients with BD diagnosis in euthymic period with lithium was showed to reduce anxiety symptoms with both agents. However, olanzapine was indicated to be relatively more effective (16). In another randomized-controlled study, it was found that adding risperidone to the treatment was not different from placebo for reducing anxiety symptoms of accompanying generalized anxiety disorder or panic disorder in patients with BD diagnosis (17). Data on the treatment of anxiety in BD with quetiapine and valproate seems to be inconsistent and contradictory. But some of the treatment guidelines recommends quetiapine and gabapentin as the first line treatment option due to their effectiveness in panic disorder and generalized anxiety disorder (18). Nevertheless, it should be kept in mind that not only pharmacotherapy, also cognitive behavioral therapy is effective and safe in these patients (19).

In conclusion, anxiety symptoms commonly accompany to the acute episodes or euthymic period of BD and negatively influence the treatment and course of illness. Although there is lack of data from randomized-controlled studies that offer specific recommendations for treatment of each anxiety disorder in BD, the primary aim should be keeping the patient euthymic. It would be better to remember cognitive behavioral therapy as a safe and effective option before pharmacological treatment. In pharmacological treatment, it is reasonable to prefer agents that are effective for the treatment of depression-mania episodes and also anxiety symptoms. Olanzapine and lamotrigine both were reported to be effective for the treatment of anxiety symptoms in euthymic period of BD. There are treatment guidelines that recommend quetiapine and gabapentin as the first-line agents particularly for their effectiveness in generalized anxiety disorder and panic disorder, although the results are inconsistent for these drugs. For the antidepressant treatment, it can be concluded that prescription of selective serotonin reuptake inhibitors (SSRI) is appropriate considering the relatively low risk of manic switch (Table 1).

Table 1. Pharmacological treatment recommendations for bipolar disorders and anxiety disorder comorbidity*

Recommendation level	Pharmacological option
First rank ¹	Gabapentin ² , Quetiapine ³
Second rank	Divalproex sodium, lamotrigine, serotonergic antidepressants ⁴ , olanzapine ³ , olanzapine-fluoxetine combination ³
Third rank	Lithium, risperidone ³ , aripiprazole ³ , pregabalin, intermediate or short-acting benzodiazepines ⁵

*Adapted from Schaffer et al. (18).

¹It is recommended to be used for anxiety symptoms after mood stabilization is achieved.

²Despite the low level of evidence, it is recommended in the first rank due to the positive risk-benefit profile based on clinical experience, particularly anxiety disorders.

³Risk of metabolic side effects should be considered and weight and metabolic parameters should be monitored in all patients prescribed new generation antipsychotics.

⁴The decision of antidepressant use should be made based on clinical knowledge about the agent's efficacy in primary anxiety disorders and patient's known mood stabilization difficulties. Particular care should be taken in adult patient with Bipolar I disorder and in young patients with a diagnosis of any bipolar subtype. Antidepressants should only be considered for the patients who are stabilized with adequate anti-(hypo)manic treatment. Among antidepressants, use of selective serotonin and noradrenaline reuptake inhibitors should be limited due to their relatively high risk of manic switch.

⁵The decision whether to use the benzodiazepines for the patient with a high risk of abuse or addiction should be done according to the short and long-term anxiolytic efficacy data of the agent in anxiety disorders. In clinical practice, it is known that anxiety symptoms can be relieved quickly for a short period with benzodiazepines. However, clinicians should carefully monitor for early physiological or psychological signs of abuse.

TREATMENT FOR COMORBID ALCOHOL-SUBSTANCE USE DISORDERS AND BIPOLAR DISORDERS

Alcohol-substance use disorders are one of the most common psychiatric comorbidity in patients diagnosed with BD. Half of the patients reported to have at least one alcohol-substance use disorders (ASUD) according to the data from United States of America (USA) (20). Literature on ASUD comorbidity in BD is limited due to the lack of comprehensive epidemiological studies in Turkey. Rates of cross-sectional regional studies are lower comparing with the rates reported from international literature. In these studies, life time alcohol use rate was found to be 32%, substance use rate was found to be 14% (21), while 12-month alcohol use disorder rate in euthymic patients with BD was 5.14% and substance use disorder was 4.11% (22). In another study done in euthymic patients with BD, it was reported that current alcohol use disorder rate was 3.2% and substance use disorder was %4.9 (23). However, in Turkey current prevalence-incidence data on dimensional classification of ASUD comorbid with BD is required considering that all of these studies were done before the diagnostic classification and criteria change in DSM-5. Consequently, ASUD accompanying to BD negatively effect the course of illness regardless of the prevalence rate of the comorbidity. In the presence of ASUD comorbidity in BD, treatment response and adherence are worse, mood episode severity and cycling are higher, quality of life and functioning level is lower (24). Furthermore, treatment of ASUD comorbidity in BD becomes more important considering the higher rates of suicide attempts in this comorbidity (25).

Treatment of BD and ASUD comorbidity can be captured in three steps as acute, continuation and maintenance phases. Main aim of the acute treatment is treatment of acute episode and stabilization of mood, detoxification of the patient from alcohol while increasing the compliance of the patient to the ASUD treatment. In the continuation and maintenance phases, it is aimed to strengthen the remission after acute episode, prevent the recurrence both BD and ASUD episodes by maintaining the sobriety (26). Lithium as first line treatment option

Table 2. Pharmacological treatment recommendations for bipolar disorders and alcohol-substance use disorders comorbidity

Recommendation level	Depression	Mania	Euthymia
First rank	Lithium, Quetiapine, Valproate	Valproate, Quetiapine	Valproate, Valproate+Naltrexone, Valproate+Disulphiram
Second rank	Lamotrigine, Olanzapine, Aripiprazole	Lithium, Carbamazepine	Lithium, Carbamazepine, Acamprosate

for the treatment of acute and maintenance phases of BD is studied in controlled and open-label studies evaluating the efficacy of it on BD comorbid with ASUD, it was showed that lithium is effective particularly alcohol use in depressive episode (26). However, data on lithium's effectiveness in substance use disorders is limited (26). There is only one 6-week controlled study indicating that lithium increased the level of functioning via decreasing the frequency of substance use (27). On the other hand, number of trials with antiepileptics which are commonly prescribed in comorbid BD is higher than lithium. In two of four prospective 6-8 weeks studies it was showed that valproate is effective for treating both mood and ASUD symptoms (28). Besides, there is only one randomized-controlled study with valproate indicating that number of alcohol drinking days decreased (29). In another study evaluating the effectiveness of treatment on substance use among rapid-cycling BD patients, it was found that lithium and valproate combination was not different from lithium monotherapy (30). In the studies done with carbamazepine which is also a mood stabilizer and antiepileptic drug, carbamazepine was found to show similar efficacy with lorazepam for controlling alcohol withdrawal while it was not effective for substance (cocaine) use disorder (26). Lamotrigine which is approved for preventing depressive recurrence in BD, was found to be effective at 300-400 mg/d dosages for improving mood symptoms and alcohol or cocaine craving in three of four studies (28). In the only randomized-controlled study with lamotrigine, after 12 weeks treatment with 400 mg/d dosage, it was found that there was no significant effect in substance use (28). In addition, randomized-controlled studies with oxcarbazepine and topiramate, which are not commonly prescribed in the treatment of BD, were not found to be effective in comorbid AUD with BD (31, 32).

New generation antipsychotics (NGA) which take place in the first line treatment in the acute and maintenance phase of BD particularly in the last decade, also commonly preferred in the treatment of ASUD comorbidity. Quetiapine, olanzapine and aripiprazole are on the top of these preferences. Quetiapine is the most studied drug among these NGA, in 8 studies between 8-20 weeks trials its efficacy was evaluated for comorbid ASUD treatment (26, 28). In four of five randomized controlled study, quetiapine was not found to be effective for alleviating mood and substance use symptoms. But in a 20-week study, it was showed that both risperidone and quetiapine was superior than placebo for decreasing craving, mood and substance use symptoms (26, 28). Quetiapine was found to be effective on mood and alcohol use symptoms in two of three open-labelled study on alcohol use disorders comorbidity while it was not effective in one study on cocaine use (26, 28). In a study with aripiprazole, it was shown to reduce craving and mood symptoms but it was not effective for alcohol/cocaine use. Olanzapine was shown to be effective for reducing both mood and ASUD symptoms (26, 28).

Number of studies with naltrexone, acamprosate and disulfiram which are approved for ASUD but not for BD, is limited. In one of two studies conducted with naltrexone, it was reported that it reduced the amount of alcohol use in patients with BD while no difference was found in the other study (26, 28). In a study evaluating the efficacy of disulfiram in patients with alcohol use disorders, it was found to be similar to naltrexone while superior to placebo in terms of days spent sober. In another study evaluating the efficacy of acamprosate in bipolar patients with alcohol use disorders, it was reported that acamprosate was found to be similar to the placebo (26, 28). Nevertheless, these treatment options might be

preferred as add-on to the treatment of BD taking their effectiveness into account on ASUD. In conclusion, quetiapine as a NGA and valproate could be considered as prominent options in the treatment of BD and ASUD comorbidity. Although there is less evidence on other treatment options listed above such as mood stabilizers, antipsychotics or treatments approved for ASUD, all can be used for appropriate patients. Motivational interviewing techniques, cognitive behavioral therapy and psychosocial support interventions at every stage of treatment are indispensable and increase the patients' well-being (26, 28).

TREATMENT FOR COMORBID OBSESSIVE-COMPULSIVE DISORDER AND BIPOLAR DISORDERS

OCD is the other common psychiatric comorbidity in BD. OCD is clinically similar to BD in terms of its illness course and episodic recurrent nature, and the diagnosis and treatment process becomes challenging when the episodes of both diseases overlap. The prevalence of OCD in BD patients has been reported in clinical and epidemiological studies in a wide range of 1.5-62% (33, 34). In a systematic review and meta-analysis, it was reported that the lifetime prevalence of OCD in BD patients was 10.9% and cross-sectional prevalence was 1.2% (35). It was also indicated that the rate of comorbidity does not differ according to the BD subtype but the rate of lifetime OCD comorbidity may decrease slightly with the age (35). Although no difference was found between bipolar subtypes, there are also findings indicating that the prevalence of OCD in manic patients is lower (9). It is claimed that lifelong and cross-sectional prevalence of BD and OCD co-occurring depends on genetic and environmental factors such as childhood traumatic life events (36, 37). It is thought that both genetic and environmental factors together cause symptoms by increasing stress sensitivity through different neurobiological pathways in limbic and cortical networks (38).

Obsessive-compulsive symptoms may occur in some of the patients with BD diagnosis during the acute mania and depression episodes. Symptoms frequently may decrease in mania/hypomania episode while it exacerbates in depression (39). OCD symptoms have negative impact on the course of illness regardless of whether accompanying acute mood episodes or not. In the co-existence of OCD and BD, more frequent recurrence of depression and increased risk of suicide risk, decreased response to the treatment and significant deterioration in social and occupational functionality are observed (40). One of the factors that worsen the clinical course in BD might be antidepressant treatment, which are used as the first-line options in OCD, induce manic switch and accelerate the mood cycling in patients with BD.

The primary aim in the treatment of BD and OCD comorbidity is mood regulation and controlling obsessive-compulsive symptoms without causing manic switch and rapid cycling. Although the use of SSRI, which is widely used in the treatment of OCD, is relatively safe in BD, they should not be used without mood stabilizers (40). If the patient is not in the manic episode and does not have a manic-switch history, adding a SSRI to the treatment in which patient is already euthymic with would be the most appropriate approach (40). Considering the possible manic-switch risk among SSRI drugs, clinicians should be careful when choosing an agent with long half-life (e.g. fluoxetine). In addition, although there are reports that paroxetine may increase lithium levels when used with lithium, sertraline and fluvoxamine seem to be relatively

safe (41). Fluvoxamine should carefully be used with antiepileptic mood stabilizers remembering its strong inhibitory effects on CYP1A2 and CYP2C19 cytochrome enzymes (41). Citalopram and escitalopram are other safe treatment options in terms of effectiveness and manic switch (40, 41). However, new generation antipsychotics (NGA) may be added to the treatment if the patient has a manic-switch history or sub-threshold manic symptoms (40, 41). Particularly olanzapine and clozapine should be carefully used that there are reports they may exacerbate the obsessive-compulsive symptoms (41). In addition to the effectiveness of NGA in the augmentation treatment of OCD, they are also reported to have mood stabilizing properties, make them preferred primarily in the comorbidity of BD and OCD (40, 41). If treatment with NGA is to be preferred; quetiapine, risperidone and aripiprazole can be used since there are positive reports with these agents (40, 41). Even though it is stated in the international treatment guidelines for BD that first generation antipsychotics can be used (40), they are not the first-line options considering the liability of bipolar patients to extrapyramidal symptoms (EPS) and the possible depressive effects on mood of these drugs.

As a result, a significant proportion of patient with BD have a diagnosis of OCD, which negatively affects course of illness. Mood stabilization should be the primary goal of treatment and addition of preferably a SSRI or NGA to the treatment for appropriate patients is recommended. In studies conducted up to date, sertraline, citalopram, escitalopram as SSRI drugs and quetiapine, risperidone, aripiprazole as NGA drugs are reported as prominent treatment options.

TREATMENT FOR COMORBID ATTENTION DEFICIT AND HYPERACTIVITY DISORDER AND BIPOLAR DISORDERS

Attention Deficit and Hyperactivity Disorder (ADHD) is a childhood-onset neurodevelopmental disorder, and it has been reported that approximately two thirds of the cases also experience symptoms in adulthood (42). Attention deficit, impulsivity and hyperactivity symptom clusters are shared in ADHD and BD, this overlap sometimes makes it difficult to differentiate clinical diagnosis (43). Although ADHD is thought to be primary diagnosis due to the early onset in childhood compared to the BD, it is observed that ADHD can be diagnosed after BD because of missing the diagnosis of ADHD in childhood (44). However, the basic clinical distinction is made according to the clinical course; ADHD is a clinical condition with chronic symptoms while BD has an episodic illness course. In studies evaluating the comorbidity of ADHD and BD in adulthood, the prevalence of ADHD comorbidity in BD was found to be 20%, and these rates are much higher in adolescence (45-48). The wide range of prevalence rates reported in clinical studies seems to depend on the study tools and design. Despite the variability in the prevalence, it has been quite consistently seen in different studies that clinical course is worse when ADHD accompanies to the BD. ADHD comorbidity was found to be associated with earlier age of onset, more depressive and mixed symptoms during acute episodes, higher rates of alcohol-substance use and poor treatment response in BD (49-51).

The risks of stimulant drugs which are among the most commonly used first-line treatment options in the treatment of ADHD, to cause manic switch and cycle acceleration in BD are the most important limiting factors in treatment. Therefore, the first rule in the treatment of patients with BD and comorbid ADHD is mood stabilization. Considering that stimulants can be effective in improving depressive symptoms in BD, both ADHD and bipolar depression can be treated with stimulant drugs. However, there is still insufficient data on the possible negative effects of stimulant use on the longitudinal course of BD after an acute depressive episode (52). On the other hand, due to the exacerbation

risk of manic-psychotic symptoms when using stimulant in acute manic episode, clinicians should be more careful in this period (53, 54). At this point, treatment guidelines may shed light on the clinical practice with the recommendations by blending limited evidence with expert consensus opinion. When Canadian Network for Mood and Anxiety Treatments (CANMAT) guideline listed the treatment options for BD and ADHD comorbidity according to the evidence level; methylphenidate and amphetamine took place in the first two rows of the list (55). Other treatment options such as CBT, venlafaxine, modafinil were listed below in the order of evidence level, while bupropion and atomoxetine were in the next ranks (55).

As a result, stimulant treatment should only be considered in the treatment of BD accompanying ADHD if bipolar patients taking a mood stabilizing agent (52). Treatment options listed from top to bottom according to the evidence level can be used with close clinical follow-up after mood stabilization. However, it is clear that long-term follow-up studies evaluating the impact of stimulant use on the clinical course of BD are required

CONCLUSION

BD is a chronic disease that has high comorbidity rates of other psychiatric disorders and causes significant disability. The most common psychiatric comorbidities are anxiety disorders, alcohol-substance use disorders, obsessive compulsive disorder and attention deficit hyperactivity disorder that all worsen the clinical course and treatment response in BD. The common basic rule for the treatment of comorbid conditions in BD is the stabilization of mood in the acute mood episodes while preventing from manic switch and cycle acceleration in long term follow-up. Within the framework of this basic primary rule, recommended agents in the treatment of other psychiatric disorders accompanying to the BD can be used.

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