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EDITORIAL

Comorbid substance use disorder in bipolar disorder: A hard rock to roll on the treatment road

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Substance use disorders (SUDs) are one of the most common psychiatric comorbidities seen in patients diagnosed with bipolar disorder (BD). It has been reported that more than half of US patients with BD had at least 1 SUD (1). The data from large-sample epidemiological studies has indicated that the risk of a SUD among patients with BD is higher than that of the general population. The National Comorbidity Survey study revealed a 10-fold higher risk of alcohol use disorder (AUD) and an 8-fold higher risk of other SUDs in patients with a diagnosis of BD (2-4). Lifetime AUD comorbidity rates have varied between BD subtypes: the percentage was higher in those with bipolar I disorder (46%) than those with bipolar II disorder (39%) (4).

In Turkey, the lack of epidemiological studies of secondary SUD in cases of BD makes it difficult to interpret the role of cultural and geographical differences on substance use in this patient group. However, the information available from cross-sectional regional studies suggest lower rates than those seen in the international literature. A lifetime alcohol use rate (distinct from AUD) of 32% and a substance use rate of 14% was observed among schizophrenic patients (5), while 5.14% of euthymic bipolar patients were recorded to have AUD and 4.11% with a different SUD in another study (6). Other research of euthymic BD patients found a current AUD rate of 3.2% and a 4.9% SUD rate (7). However, all of these data were collected before the current SUD criteria were added to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, published in 2013. Updated research about the current prevalence and incidence rates in our country is needed in order to make informed comments and provide the optimal treatment.

The high SUD comorbidity rate in BD has a strongly negative impact on the course of illness and also presents a significant treatment challenge. BD patients with an accompanying SUD diagnosis have been seen to have an earlier age of illness onset and a higher rate of psychotic features in the first episode than cases without a secondary disorder (8,9). In addition, it has been observed that patients with BD and an accompanying SUD have a faster onset and longer duration of mood episodes as well as a shorter duration of remission intervals between episodes (8,9). Patients with BD have also been reported to have more depressive episodes and a higher rate of suicide attempt (10,11). All of these prognostic factors are strongly related to lower life satisfaction and functioning as a result of the increased burden of subthreshold interepisodic residual symptoms and a more severe illness subtype. Consequently, a careful and thoughtful consideration of appropriate treatment options in cases of BD with an accompanying SUD is crucial to achieving adequate mood regulation and preventing subsequent episodes and other potential consequences.

Treatment of BD with a SUD comorbidity includes 3 stages: the acute, continuation, and maintenance phases. The primary aim of acute treatment is management of an acute episode, with stabilization of mood,

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detoxification, and promoting patient compliance with SUD treatment. The goal of the continuation and maintenance phases is to strengthen remission and sobriety and prevent the recurrence of both BD and SUD episodes (12). Lithium has been studied in controlled and open-label studies as a first-line treatment option for the acute and maintenance phases of BD with a comorbid SUD, and it has been shown to be particularly effective in cases of patients with AUD experiencing a depressive episode (12). However, data on the effectiveness of lithium in SUD other than excessive alcohol use are limited (12). The results of a 6-week controlled study of adolescents indicated that lithium was a successful treatment of both disorders (13). More research has focused on the use of antiepileptics. In 2 of 4 prospective studies of 6-8 weeks duration, valproate was reported to be effective for treating both mood and SUD symptoms (14). One randomized-controlled study of valproate indicated that the number of days of heavy alcohol consumption and the number of drinks decreased (15). In another study evaluating the effectiveness of treatment of substance use among rapid-cycling BD patients, it was found that the results of a combination of lithium and valproate were not significantly different from lithium monotherapy (16). Carbamazepine, another mood stabilizer and antiepileptic drug, has been found to demonstrate a similar efficacy to lorazepam in controlling alcohol withdrawal, but was not effective in cocaine users (12). Lamotrigine, which is approved for preventing depressive recurrence in BD, was found to improve mood symptoms and alcohol or cocaine cravings at a dosage of 300-400 mg/day in 3 of 4 studies examined in a review (14). However, the only randomized-controlled study to analyze lamotrigine use revealed no significant effect on substance use after 12 weeks of treatment with 400 mg/day (14). In addition, randomized-controlled studies of oxcarbazepine and topiramate, which are not commonly prescribed in the treatment of BD, were not found to be effective in BD with secondary AUD (17,18).

New-generation antipsychotics (NGAs), such as quetiapine, olanzapine, and aripiprazole, have particularly been used in first-line treatment for the acute and maintenance phases of BD in the last decade, and are also commonly used to treat an SUD comorbidity. Quetiapine is perhaps the most studied NGA. The efficacy in comorbid SUD treatment was evaluated in 8 studies that include trials of 8-20 weeks (12,14). In 4 of the 5 randomized controlled studies, quetiapine was not found to provide effective alleviation of mood and SUD symptoms. However, the results of a 20-week study indicated that treatment with risperidone and quetiapine was superior to a placebo in reducing cravings, and other mood and SUD symptoms (12,14). Quetiapine was found to have a valuable effect on mood and AUD symptoms in 2 of 3 open-label studies of AUD comorbidity, though it was not considered sufficiently successful in cases of cocaine use (12,14). A study of the use of aripiprazole revealed that while it reduced some cravings and mood symptoms, it was not sufficiently effective for alcohol or cocaine use. Olanzapine successfully reduced both mood and SUD symptoms (12,14).

The number of studies that have evaluated the use of naltrexone, acamprosate, or disulfiram, which are approved for AUD but not for BD, is limited. One of 2 studies of naltrexone reported that it reduced alcohol use in patients with BD, while the other recorded no significant difference (12,14). In research evaluating the efficacy of disulfiram in patients with AUD, it was found to be similar to naltrexone while superior to a placebo in terms of days spent sober. Another study evaluated the effectiveness of acamprosate in BD patients with AUD and it was reported that acamprosate results were similar to those of a placebo (12,14). Nevertheless, these treatment options might serve as add-on treatment options in cases of BD with AUD. Quetiapine and valproate may be initial choices in the treatment of BD with an SUD comorbidity. Although the evidence on other treatment options remains slim, mood stabilizers, antipsychotics, or other treatments approved for SUD can be used in appropriate cases. Motivational interviewing, cognitive behavioral therapy, and other psychosocial support interventions at every stage of treatment are indispensable and should be a component in efforts to increase the patients' well-being (12,14).

In conclusion, the current findings related to evidence-based treatment options approved with randomized-placebo controlled studies remain insufficient, despite the high global prevalence of an SUD comorbidity with BD. The exclusion of a presence of SUD in BD trials likely contributed to the limited available data. Additional acute and long-term follow-up trials of pharmacological treatment options for BD and SUD comorbidities are needed to improve the available level of evidence. Currently, a combination of mood stabilizers, NGAs, and other pharmacological agents approved for the treatment of SUD have been reported to be effective in the literature. Publication of specific treatment guidelines for comorbid SUD in BD patients would help clinicians to roll this rock from the long, often bumpy, road of the treatment journey.

REFERENCES

1. Messer T, Lammers G, Müller-Siecheneder F, Schmidt RF, Latifi S. Substance abuse in patients with bipolar disorder: A systematic review and meta-analysis. Psychiatry Res 2017; 253:338-350.
2. Kessler RC, Crum RM, Warner LA, Nelson CB, Schulenberg J, Anthony JC. Lifetime co-occurrence of DSM-III-R alcohol abuse and dependence with other psychiatric disorders in the National Comorbidity Survey. Arch Gen Psychiatry 1997; 54:313-321.
3. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. Arch Gen Psychiatry 2005; 62:593-602. [CrossRef]
4. Regier DA, Farmer ME, Rae DS, Locke BZ, Keith SJ, Judd LL, et al. Comorbidity of mental disorders with alcohol and other drug abuse. Results from the Epidemiologic Catchment Area (ECA) Study. JAMA 1990; 264:2511-2518. [CrossRef]
5. Tekin Uludag Y, Gulec G. Prevalence of substance use in patients diagnosed with schizophrenia. Noro Psikiyatr Ars 2016; 53:4-11.
6. Umut G, Arslan Delice M, Cansiz A, Can A, Kurt E, Evren C. Clinical characteristics of euthymic bipolar disorder patients comorbid with alcohol and drug use disorders and psychometric properties of the assessment tools. Bulletin of Clinical Psychopharmacology 2016; 26:48-57. [CrossRef]
7. Akkaya C, Altin M, Kora K, Karamustafalioglu N, Yasan A, Tomruk N, et al. Sociodemographic and clinical features of patients with bipolar i disorder in Turkey-HOME study. Bulletin of Clinical Psychopharmacology 2012; 22:31-42. [CrossRef]
8. Pacchiarotti I, Di Marzo S, Colom F, Sánchez-Moreno J, Vieta E. Bipolar disorder preceded by substance abuse: a different phenotype with not so poor outcome? World J Biol Psychiatry 2009; 10:209-216. [CrossRef]
9. Ostacher MJ, Perlis RH, Nierenberg AA, Calabrese J, Stange JP, Salloum I, et al; STEP-BD Investigators. Impact of substance use disorders on recovery from episodes of depression in bipolar disorder patients: prospective data from the Systematic Treatment Enhancement Program for Bipolar Disorder (STEP-BD). Am J Psychiatry 2010; 167:289-297. [CrossRef]
10. Cerullo MA, Strakowski SM. The prevalence and significance of substance use disorders in bipolar type I and II disorder. Subst Abuse Treat Prev Policy 2007; 2:29. [CrossRef]
11. Dalton EJ, Cate-Carter TD, Mundo E, Parikh SV, Kennedy JL. Suicide risk in bipolar patients: the role of co-morbid substance use disorders. Bipolar Disord 2003; 5:58-61. [CrossRef]
12. Altinbas K, Evren C. Pharmacotherapy options in comorbid bipolar disorder and alcohol-substance use disorders. Bulletin of Clinical Psychopharmacology 2013; 23:378-389. [CrossRef]
13. Geller B, Cooper TB, Sun K, Zimerman B, Frazier J, Williams M, et al. Double-blind and placebo-controlled study of lithium for adolescent bipolar disorders with secondary substance dependency. J Am Acad Child Adolesc Psychiatry 1998; 37:171-178. [CrossRef]
14. Coles AS, Sasiadek J, George TP. Pharmacotherapies for co-occurring substance use and bipolar disorders: A systematic review. Bipolar Disord 2019; 21:595-610. [CrossRef]
15. Salloum IM, Cornelius JR, Daley DC, Kirisci L, Himmelhoch JM, Thase ME. Efficacy of valproate maintenance in patients with bipolar disorder and alcoholism: a double-blind placebo-controlled study. Arch Gen Psychiatry 2005; 62:37-45. [CrossRef]
16. Kemp DE, Gao K, Ganocy SJ, Elhaj O, Bilali SR, Conroy C, et al. A 6-month, double-blind, maintenance trial of lithium monotherapy versus the combination of lithium and divalproex for rapid-cycling bipolar disorder and Co-occurring substance abuse or dependence. J Clin Psychiatry 2009; 70:113-121. [CrossRef]
17. Koethe D, Juelicher A, Nolden BM, Braunwarth WD, Klosterkötter J, Niklewski G, et al. Oxcarbazepine--efficacy and tolerability during treatment of alcohol withdrawal: A double-blind, randomized, placebo-controlled multicenter pilot study. Alcohol Clin Exp Res 2007; 31:1188-1194. [CrossRef]
18. Sylvia LG, Gold AK, Stange JP, Peckham AD, Deckersbach T, Calabrese JR, et al. A randomized, placebo-controlled proof-of-concept trial of adjunctive topiramate for alcohol use disorders in bipolar disorder. Am J Addict 2016; 25:94-98. [CrossRef]