INTRODUCTION

Patients with bipolar I disorder frequently have alcohol dependence as a comorbid psychiatric disease (23%-38%)\(^1\)-\(^3\). Various evidence-based pharmacological options are available for the treatment of bipolar I disorder\(^4\), among which aripiprazole and its long-acting injection (ALAI) are reportedly efficacious for preventing manic episodes\(^5\),\(^6\). However, only a few drugs are available for the treatment of alcoholism, including acamprosate, naltrexone, and disulfiram; whether aripiprazole can treat alcohol dependence remains controversial\(^7\),\(^8\).

While nearly all patients with bipolar I disorder require long-term medication to prevent relapse and recurrence, adherence to pharmacological treatment among patients with bipolar disorder is reportedly low\(^9\); limited adherence to medical treatment also characterizes patients with alcohol dependence\(^10\). Resolving poor adherence to medical treatment in patients with bipolar disorder or alcohol dependence thus warrants investigation.

Here, we describe a patient diagnosed with bipolar I disorder and a comorbid diagnosis of alcohol dependence.

CASE

A 47-year-old woman had recurrent depressive episodes with appetite loss, self-harm behavior, suicidal ideation, and anxiety symptoms.
including panic attacks, from her late teens. At the age of 35 years, she first visited a psychiatric clinic and was diagnosed with major depressive disorder; she began taking paroxetine but continued to experience recurrent depressive episodes. Moreover, she began to engage in heavy alcohol consumption at approximately 39 years of age. She was referred to our hospital at the age of 40 years. Despite attempts to treat her alcoholism with acamprosate (1998 mg/day) and our hospital’s alcoholism treatment program, she was hospitalized three times due to alcohol withdrawal delirium. Deterioration of her liver function was evinced by the following laboratory findings when she engaged in the heaviest alcohol consumption: serum aspartate transaminase glutamate oxaloacetate transaminase, 549 IU/L; alanine transaminase glutamic pyruvic transaminase, 132 IU/L; and gamma-glutamyl transpeptidase, 794 IU/L.

At the age of 43 years, her behavior evinced a first manic episode: feelings of grandiosity, increased talkativeness, and grandiose delusions. We therefore diagnosed her with bipolar I disorder comorbid with alcohol dependence. Regarding pharmacotherapy for her bipolar I disorder, we sought to manage the depressive and/or manic symptoms with the following atypical oral antipsychotic monotherapies: quetiapine, 500 mg/d; olanzapine, 10 mg/d, and combination therapies of antipsychotics plus mood stabilizers: valproate, 1000 mg/d; and carbamazepine 400 mg/d when she was in hospital. Although these pharmacotherapies allowed temporary remission, which satisfied the section of bipolar and related disorders in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5), of her bipolar symptoms, such that she could be discharged, her adherence to medical treatments did not improve; they did not improve her adherence to medical treatments. After the patient had been diagnosed with bipolar I disorder, she was hospitalized an additional four times due to depressive or manic episodes with psychosis because of poor adherence to the prescribed regimen. We did not prescribe lithium because of her history of hypothyroidism, for which she was undergoing treatment during the same period.

When the patient was hospitalized for the eighth time due to manic episodes accompanied by heavy drinking at the age of 44 years, we attempted to treat her with LAI, followed by pharmacotherapy with oral aripiprazole tablets at a maximum daily dosage of 30 mg/d. After explaining to the patient and her family that LAI was an off-label therapy for bipolar disorder in Japan, we obtained consent from both to perform LAI treatment. We first began prescription of LAI at a dose of 400 mg/mo intramuscularly (LAI 400), in combination with acamprosate, 1998 mg/d. Neither drug-induced any adverse events in the patient. Three months after commencing LAI treatment, the patient was discharged from our hospital due to remission of her bipolar symptoms. She regularly returned to the outpatient department of our hospital for follow-up visits. Over the following 2 years, she maintained sobriety, did not crave alcohol, and did not have any recurrent mood episodes. In addition, her thyroid function was well controlled before and after LAI treatment. After her last discharge, she obtained a teacher qualification and has been employed as a full-time worker.

3 DISCUSSION

We herein report the case of a 47-year-old woman with bipolar I disorder and alcohol dependence characterized by resistance to pharmacotherapy for bipolar disorder, as well as resistance to our hospital’s alcoholism treatment program and acamprosate for alcohol dependence. To the best of our knowledge, this is the first report to demonstrate the successful concurrent management of bipolar I disorder and alcohol dependence with LAI 400.

Accumulating evidence suggests that dysregulation in the mesolimbic dopamine system is involved in the pathophysiology of alcoholism11-13. Previous animal and human studies have reported that aripiprazole, which acts as a partial agonist of dopamine D2 receptors, can potentially treat alcohol dependence14-16. However, two randomized clinical trials have found conflicting results regarding the efficacy of aripiprazole in addressing alcohol dependence7,8.

The first randomized placebo-controlled study with a sample of 295 patients found that an aripiprazole regimen, in which the drug was initiated at 2 mg/d and titrated to 30 mg/d over the course of 28 days, failed to achieve a significant percentage of abstinent days among patients with alcohol dependence in a 12-week period7; the authors of that study proposed that the high incidence of dropout patients, aripiprazole group (40.3%) vs placebo group (26.7%), who were treated with a daily aripiprazole dosage of more than 15 mg influenced the primary outcome of their study7. The second double-blind trial that compared the efficacy of a flexible dosage of aripiprazole (5-15 mg/d) to that of a fixed dosage of naltrexone (50 mg/d) in treating alcohol dependence showed that aripiprazole and naltrexone similarly affected remaining abstinence and craving for alcohol8. In addition, a placebo-controlled study found that oral aripiprazole treatment administered at a maximum dosage of 15 mg/d reduced drinking in alcoholic patients with low impulse control more effectively than in those without low impulse control17.

Considering the aforementioned evidence of the capacity LAI to prevent relapse in patients with bipolar I disorder, moderate dosages of aripiprazole treatment may help to improve maintenance treatment of bipolar disorder and the management of alcohol abstinence, as was observed in the present case; however, the precise equivalent dose of oral aripiprazole tablets administered daily that will achieve the same effect as LAI 400 is unclear.

In addition, switching from oral antipsychotics to LAI antipsychotics is reportedly effective in promoting adherence among patients with psychotic disorders18. Thus, in pharmacological treatments of bipolar disorders and alcohol dependence, LAI treatment may improve relapse prevention in patients with poor adherence to pharmacotherapy.

4 CONCLUSION

Considering that bipolar disorders are frequently comorbid with alcohol dependence, our findings in this case indicated that LAI may
be an efficacious option for the treatment of patients with bipolar disorder and alcohol dependence who respond well to oral aripiprazole and experience repeated relapse due to poor adherence to medical treatment. Further clinical trials are needed to validate our findings.

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CONFLICT OF INTEREST

T.K. has received honoraria as a speaker/consultant from Dainippon Sumitomo, Otsuka, Nihon Shinyaku, and Yoshitomiyakuhin. T.H. has received personal fees from research support of a clinical trial managed by a global bracket company. H.S. has received honoraria as a speaker from Daiichi-Sankyo and Janssen.

AUTHOR CONTRIBUTIONS

T.K. was the consulting psychiatrist for the patient. T.H. and H.S. supervised T.K. in the treatment of the patient. All authors contributed to the writing and revision of the manuscript, and all authors have read and approved the submitted version of the manuscript.

INFORMED CONSENT

The patient provided written informed consent for the publication of this case report. The treatment in this case report was performed in accordance with the World Medical Association's Declaration of Helsinki.

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REFERENCES

1. Merikangas KR, Akiskal HS, Angst J, Greenberg PE, Hirschfeld RMA, Petukhova M, et al. Lifetime and 12-month prevalence of bipolar spectrum disorder in the National Comorbidity Survey replication. Arch Gen Psychiatry. 2007;64(5):543–52.

2. Frye MA, Altschuler LL, McElroy SL, Suppes T, Keck PE, Denicoff K, et al. Gender differences in prevalence, risk, and clinical correlates of alcoholism comorbidity in bipolar disorder. Am J Psychiatry. 2003;160(5):883–9.

3. Chengappa KN, Levine J, Gershon S, Kuper DJ. Lifetime prevalence of substance or alcohol abuse and dependence among subjects with bipolar I and II disorders in a voluntary registry. Bipolar Disord. 2000;2(3 Pt 1):191–5.

4. Soyka M, Kranzer HR, Hesselbrock V, Kasper S, Mutschler J, Möller H-J. Guidelines for biological treatment of substance use and related disorders, part 1: alcoholism, first revision. World J Biol Psychiatry. 2017;18(2):86–119.

5. Fountoulakis KN, Grunke H, Vieta E, Young A, Yatham L, Blatrix P, et al. The International College of Neuro-Psychopharmacology (CINP) treatment guidelines for bipolar disorder in adults (CINP-BD-2017), part 3: the clinical guidelines. Int J Neuropsychopharmacol. 2017;20(2):196–205.

6. Calabrese JR, Sanchez R, Jin Na, Amatniek J, Cox K, Johnson B, et al. Efficacy and safety of aripiprazole once-monthly in the maintenance treatment of bipolar I disorder: a double-blind, placebo-controlled, 52-week randomized withdrawal study. J Clin Psychiatry. 2017;78(3):324–31.

7. Anton RF, Kranzer H, Breder C, Marcus RN, Carson WH, Han J. A randomized, multicenter, double-blind, placebo-controlled study of the efficacy and safety of aripiprazole for the treatment of alcohol dependence. J Clin Psychopharmacol. 2008;28(1):5–12.

8. Martinotti G, Di Nicola M, Di Giannantonio M, Janiri L. Aripiprazole in the treatment of patients with alcohol dependence: a double-blind, comparison trial vs. naltrexone. J Psychopharmacol. 2009;23(2):123–9.

9. Jawad I, Watson S, Haddad PM, Talbot PS, McAllister-Williams RH. Medication nonadherence in bipolar disorder: a narrative review. Ther Adv Psychopharmacol. 2018;8(12):349–63.

10. Dermody SS, Wardell JD, Stoner SA, Hendershot CS. Predictors of daily adherence to naltrexone for alcohol use disorder treatment during a mobile health intervention. Ann Behav Med. 2018;52(9):787–97.

11. Heinz A, Siessmeier T, Wrase J, Hermann D, Klein S, Grüsser SM, et al. Correlation between dopamine D(2) receptors in the ventral striatum and central processing of alcohol cues and craving. Am J Psychiatry. 2004;161(10):1783–9.

12. Hirth N, Meinhardt MW, Noori HR, Salgado H, Torres-Ramirez O, Uhrig S, et al. Convergent evidence from alcohol-dependent humans and rats for a hyperdopaminergic state in protracted abstinence. Proc Natl Acad Sci U S A. 2016;113(11):3024–9.

13. Haass-Koffler CL, Leggio L, Kenna GA. Pharmacological approaches to reducing craving in patients with alcohol use disorders. CNS Drugs. 2014;28(4):343–60.

14. Ingman K, Kupila J, Hytti H, Korpi ER. Effects of aripiprazole on alcohol intake in an animal model of high-alcohol drinking. Alcohol Alcohol. 2006;41(4):391–8.

15. Han DH, Kim SM, Choi JE, Min KJ, Renshaw PF. Adjunctive aripiprazole therapy with escitalopram in patients with co-morbid major depressive disorder and alcohol dependence: clinical and neuroimaging evidence. J Psychopharmacol. 2013;27(3):282–91.

16. Myrick H, Li X, Randall PK, Henderson S, Voronin K, Anton RF. The effect of aripiprazole on cue-induced brain activation and drinking parameters in alcoholics. J Clin Psychopharmacol. 2010;30(4):365–72.

17. Voronin K, Randall P, Myrick H, Anton R. Aripiprazole effects on alcohol consumption and subjective reports in a clinical laboratory paradigm—possible influence of self-control. Alcohol Clin Exp Res. 2008;32(11):1954–61.

18. Kishi T, Oya K, Iwata N. Long-acting injectable antipsychotics for the prevention of relapse in patients with recent-onset psychotic disorders: a systematic review and meta-analysis of randomized controlled trials. Psychiatry Res. 2016;246:750–5.

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