Successful discontinuation of oxycodone under pramipexole treatment for restless legs syndrome due to withdrawal

Letter to the Editor

Successful discontinuation of oxycodone under pramipexole treatment for restless legs syndrome due to withdrawal

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Oxycodone is a semi-synthetic opioid used to relieve severe pain. Opioid withdrawal is associated with both physical discomfort and psychological symptoms, which can impede opioid tapering. Restless legs syndrome (RLS), a common opioid withdrawal symptom, occurs in approximately 50% of patients during opioid tapering.[1] Although some treatments have been recommended for general restlessness associated with opioid withdrawal,[2] no treatment has been recommended for opioid withdrawal-induced RLS. Here, we report a case in which pramipexole was administered to treat RLS during oxycodone tapering, which improved the burning sensation in both legs and restlessness and allowed oxycodone to be discontinued. Written informed consent from the patient was obtained for both research and publication. **This case report is conformed to the provisions of the Ethics Committee of the Hamamatsu University School of Medicine and Declaration of Helsinki.**

A 17-year-old Japanese man visited the department of internal medicine in our hospital, complaining of severe left thigh pain and weight loss. He was generally healthy, with no history of major illness, smoking or illegal drug use, or mental illness. He was diagnosed with chronic myelogenous leukemia (CML), based on Philadelphia chromosome detection. His thigh pain was suspected to be caused by extramedullary blast crisis of CML. Therefore, oxycodone administration was started to alleviate his severe pain. Molecularly targeted therapy was started to treat CML. After 7 months of treatment, the CML achieved a complete cytogenetic response, and his thigh pain disappeared. Therefore, oxycodone tapering was initiated. However, when

oxycodone was tapered, he complained of burning in **the entire region of the thighs and lower legs on both sides**, restlessness, and the urge to move when at rest, especially in the evening, leading to oxycodone misuse. Approximately three years after oxycodone treatment began, the dosage had increased to 90 mg/day, which exceeds the maximum usage approved in Japan. He was introduced to the department of psychiatry and diagnosed with opioid use disorder, according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Diazepam and clonazepam were used to treat the burning sensation in his legs and the restlessness, on an outpatient basis; however, his symptoms did not improve. Therefore, he was admitted to the psychiatric ward of our hospital, at the age of 20 years. No abnormalities were found during the physical examination or laboratory test results, including ferritin, hemoglobin, and serum iron levels. **Family history for RLS was negative**. Because his discomfort symptoms met the RLS criteria,[3] he was diagnosed with RLS due to oxycodone withdrawal. His International RLS Study Group Rating Scale (IRLS) score was 31, indicating severe RLS. Pramipexole administration (0.25 mg/day) was started to treat RLS, and oxycodone was linearly decreased, at a rate of 5 mg/3-4 days, based on previous literature.[4] Three weeks after the start of pramipexole administration, the IRLS score improved to 10, indicating mild RLS, and oxycodone was reduced to 60 mg/day. Although he was allowed to remain at home for two weeks, his oxycodone misuse recurred while at home. Therefore, pramipexole was increased to 0.75 mg/day, which maintained the IRLS score near 10. Six weeks later, oxycodone was discontinued, without any

other withdrawal symptoms. RLS completely disappeared 3 days after oxycodone discontinuation. After discharge, pramipexole was gradually tapered, at a rate of 0.25 mg/week, on an outpatient basis. Three weeks later, pramipexole was discontinued. No recurrent RLS has been reported for the past two months.

This is the first report to show that pramipexole administration can relieve RLS symptoms during oxycodone withdrawal, allowing oxycodone to be discontinued. **Our experience suggests that pramipexole has potential for the treatment of RLS during opioid withdrawal without causing serious adverse events. However, clinicians must carefully monitor the any expected risks with consulting specialists when using pramipexole in patients with opioid use disorders. Pramipexole is a selective D2/3 dopamine agonist.[5] Impulse control disorders, which are well-known adverse events associated with dopamine agonist use,[6] as well as obsessive-compulsive disorder can exacerbate certain behavioral aspects of addiction. Positron emission tomography studies have shown that opioid addiction is associated with decreased D2 receptor expression,[7] and low D2/3 receptor binding.[8] These dopamine dysfunctions associated with long-term opioid use may increase the incidence of augmentation. Impulse control disorders have been identified as risk factors for dopamine withdrawal syndrome.[9] The use of low-dose pramipexole during RLS treatment is important for preventing both augmentation and dopamine withdrawal syndrome.[9,10] Our experience also suggests that RLS due to opioid withdrawal, which can**

be observed during the daytime and difficult to identify the worsening during the evening, is difficult to distinguish from RLS-like symptoms. When treating RLS during opioid tapering, RLS must be properly distinguished from RLS-like symptoms according to the diagnostic criteria.[3]

Disclosure statement

The authors declare no conflict of interest.

References

1. Mackie SE, McHugh RK, McDermott K, Griffin ML, Winkelman JW, Weiss RD. Prevalence of restless legs syndrome during detoxification from alcohol and opioids. *J Subst Abuse Treat*. 2017; **73**: 35-39.
2. Schuckit MA. Treatment of Opioid-Use Disorders. *N Engl J Med*. 2016; **375**: 357-68.
3. Allen RP, Picchietti DL, Garcia-Borreguero D *et al*. Restless legs syndrome/Willis-Ekbom disease diagnostic criteria: updated International Restless Legs Syndrome Study Group (IRLSSG) consensus criteria--history, rationale, description, and significance. *Sleep Med*. 2014; **15**: 860-73.

4. Berna C, Kulich RJ, Rathmell JP. Tapering Long-term Opioid Therapy in Chronic Noncancer Pain: Evidence and Recommendations for Everyday Practice. *Mayo Clin Proc*. 2015; **90**: 828-42.

5. Winkelman JW, Armstrong MJ, Allen RP *et al*. Practice guideline summary: Treatment of restless legs syndrome in adults: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology*. 2016; **87**: 2585-2593.

6. Grall-Bronnec M, Victorri-Vigneau C, Donnio Y *et al*. Dopamine Agonists and Impulse Control Disorders: A Complex Association. *Drug Saf.* 2018; **41**:19-75.

7. Wang GJ, Volkow ND, Fowler JS *et al*. Dopamine D2 receptor availability in opiate-dependent subjects before and after naloxone-precipitated withdrawal. *Neuropsychopharmacology*. 1997; **16**: 174-82.

8. Martinez D, Saccone PA, Liu F *et al*. Deficits in dopamine D(2) receptors and presynaptic dopamine in heroin dependence: commonalities and differences with other types of addiction. *Biol Psychiatry*. 2012; **71**: 192-8.

9. Yu XX, Fernandez HH. Dopamine agonist withdrawal syndrome: A comprehensive review. *J Neurol Sci*. 2017; **374**: 53-55.

10. Takahashi M, Nishida S, Nakamura M *et al*., Restless legs syndrome augmentation among Japanese patients receiving pramipexole therapy: Rate and risk factors in a retrospective study. *PLoS One*. 2017; **12**: e0173535.