

# Doxazosin improved COVID-19 associated nightmare in a patient with major depressive disorder: a case report with a positive rechallenge

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**This article reports on the treatment of a patient with nightmares who was treated with doxazosin of an alpha 1-adrenergic antagonists. A 71-year-old Japanese major depressive disorder (MDD) woman experienced nightmares after the coronavirus disease 2019 pandemic. She had nightmares about being chased by a coronavirus and catching the corona virus. After adding doxazosin 1 mg daily in the morning, her nightmares led to remission without side effects. We also had a rechallenge regimen with doxazosin. The nightmares ceased on the second night of the rechallenge and did not return with continued treatment. This case report suggests that doxazosin may be a useful therapeutic option to target nightmares**

## Introduction

In late February 2020, the pandemic of the coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus 2. The pandemic of the COVID-19 might be regarded as a stressful event in common mental disorders including major depressive disorder (MDD).

Nightmares are defined as extremely frightening dreams from which a person wakes up directly. Nielsen and Zadra estimated a prevalence rate of around 4–8% of the general population (Nielsen and Zadra, 2000). Patients with remitted MDD have an estimated prevalence rate of 9.3% (Li et al., 2012). Nightmares were reported to be related to suicidality, regardless of MDD, in a 2005 study (Bernert et al., 2005). The most effective treatments reported in the literature were either cognitive-behavior treatment or pharmacological interventions.

The rationale for the use of pharmacologic reduction of central nervous system adrenergic activity in the treatment of post traumatic stress disorder (PTSD) has recently been reviewed by Boehnlein and Kinzie (2007). Prazosin is an  $\alpha$ 1-adrenergic receptor antagonist introduced as an antihypertensive agent. Some previous meta-analyses showed prazosin improved nightmares in patients with PTSD (George et al., 2016; Khachatryan et al., 2016; Singh et al., 2016; Zhang et al., 2020). Nonpharmacological treatment, psychological interventions, imagery rehearsal therapy, and cognitive-behavioral therapy also improved nightmares in adults (Casement and Swanson, 2012; Barrera et al., 2013; Ho et al., 2016; Yücel et al., 2020). There are some case reports

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of the effects of trazodone on nightmares in patients with advanced cancer (Tanimukai et al., 2013) and prazosin on nightmares in patients with substance abuse disorders (Aggarwal and Lindegaard, 2020).

Herein, we report the case of a patient with remitted MDD with marked nightmares associated with COVID-19 who was successfully treated by doxazosin. This case report might suggest an alternative treatment for nightmares.

The patient was given informed consent, and their anonymity was preserved.

## Case report

A 71-year-old Japanese woman was admitted for psychiatric outpatient maintenance treatment because of MDD.

After she retired from her job at the age of 65, she had spent time enjoying tennis and Karaoke. At age 69, the patient presented the characteristic symptoms of depressed mood, loss of interest, insomnia, loss of body weight, and feelings of hopelessness for 2 months. She was diagnosed MDD according to DSM-5. The 17-item Hamilton Rating Scale for Depression (Ham-D) total score was 21 and initial laboratory blood tests, including thyroid function, revealed normal ranges. Initially, the patient was treated with escitalopram, 10 mg/day, for 21 days. She also had begun using eszopiclone (1 mg/day) to treat insomnia. Depressed mood was improved, and the Ham-D total score improved to 6. She had continued antidepressant treatment for 2 years and the depressive symptoms were stable. The patient had a history of hypertension 4 years ago. She has been taking nifedipine

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5 mg daily at morning for the past 4 years with good effect. The patient was diagnosed with breast cancer five years ago and had a mastectomy followed by adjuvant chemotherapy and hormonal therapy. She had no signs of recurrence. The patient was a housewife and had no alcohol or drug abuse.

In March 2020, she experienced nightmares and abnormal dreams in the COVID-19 pandemic without worsening depressive symptoms. There is no identified traumatic event that might suggest PTSD. She had nightmares about being chased by a coronavirus and catching a coronavirus. She was terrified that she might be infected with coronavirus in her dreamlike state. The nightmares caused severe sleep disturbances and troublesome daytime irritability. Despite acceptable control of diurnal symptoms, nightmares remained virtually unchanged, causing sweating and a choking sensation. The Ham-D showed negative results for depressive symptoms. Physical examination showed that the patient was overweight but examinations were otherwise unremarkable. Liver enzymes, kidney function (creatinine, blood urea nitrogen), and urea were within normal limits. However, her blood pressure increased in March 2020.

We prescribed trazodone 50 mg per night and eszopiclone 2 mg per night. Nightmares remained virtually unchanged. Treatment with risperidone 1 mg per night was attempted, but had to be stopped due to extrapyramidal symptoms.

Physician added doxazosin 1 mg daily in the morning (starting dose 0.5 mg/day) for her hypertension. The benefits began to be evident in the two weeks. The patient's baseline blood pressure figures were around 145–95 mmHg. When the fully effective dose for the remission of nightmares was reached, average daytime blood pressure figures fell to 125–80 mmHg, with no symptoms of dizziness, syncope, or any other noticeable adverse effect. No other psychotropic medications were started.

In an attempt to evaluate the causality of the nightmare and abnormal dreams, the patient agreed to temporarily discontinue and rechallenge doxazosin. Doxazosin was stopped abruptly, but withdrawal symptoms did not occur. With doxazosin medication discontinuation, her nightmares quickly recurred. She had nightmares most days after discontinuing the doxazosin.

The patient resumed doxazosin treatment and after 4 days, again reported resolution of the nightmares. The patient was seen for follow-up evaluation 2 weeks later. At that time, she reported a complete resolution of the nightmares. Therefore, no increase in the doxazosin was required. The follow-up evaluation 1 month later revealed continued remission of nightmares and improved sleep.

## Discussion

This is the first case, to our knowledge, reporting nightmares associated with COVID-19 improved by doxazosin in a patient with stable MDD. Doxazosin is a nonsedating alpha1-adrenergic antagonist, used in the treatment of hypertension. Excessive noradrenergic activity in the central nervous system is associated with sleep disturbance, a characteristic of PTSD (Raskind et al., 2013). The noradrenergic system is thought to have the leading role in fear memory formation, consolidation, and especially recalling which is associated with sleep disturbances and nightmares observed in PTSD (De Berardis et al., 2015). Thus, the modulation of the noradrenergic system is suggested to be an effective strategy in treating sleep disturbances.

Although both prazosin and doxazosin are alpha1-adrenergic antagonists, there are differences between them. Prazosin is a highly lipophilic alpha1-receptor antagonist; as such, it enters the brain more easily from the blood and is centrally active (Miller, 2008). Prazosin is well absorbed but undergoes substantial first-pass metabolism. It has a short half-life of 2–3 h and reaches peak plasma concentrations within 1–2 h. Doxazosin has a long half-life (16–30 h), allowing not only easy dosage but maintenance of effect throughout the night. Its also good absorption profile reduces the risk of hypotension. All of these characteristics positively differentiate doxazosin from its analog, prazosin, which has been described as an efficacious adjuvant treatment for nightmares. The adverse effect profiles of prazosin and doxazosin are similar; adverse effects tend to be infrequent and mild, and can include dizziness, palpitations, headache, and fatigue.

This case report suggests that doxazosin may be a useful therapeutic option to target nightmares in individuals who do not typically take sleep medication. The limited data currently available in the literature suggest that there may be a role for doxazosin in the treatment of nightmares; however, there are currently no placebo-controlled, double-blind studies or longer-term studies to assess its efficacy and tolerability for this use. More studies would help determine if doxazosin is a viable alternative to prazosin for the treatment of nightmares.

## Acknowledgements

### Conflicts of interest

There are no conflicts of interest.

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