

# Doxazosin for the treatment of nightmare disorder: A diary-based case study

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## Abstract

The  $\alpha_1$ -adrenergic antagonist prazosin has showed good effect against posttraumatic stress disorder–related nightmares in several randomized controlled trials. The  $\alpha_1$ -adrenergic antagonist doxazosin, which has a longer half-life than prazosin, has received far less attention in the treatment of such nightmares. Here, we report a case of a patient suffering from severe nightmares following an erroneous medical administration of adrenaline (causing severe physiological hyper-activation) who was treated with doxazosin. Over a period of 280 days, the patient kept a nightmare diary and took 0, 4, or 8 mg doxazosin. The analyses showed that 8 mg doxazosin (55.2% nightmare-free nights) worked better (odds ratio = 28.2; 95% confidence interval = 3.7–213.9) compared to nights without doxazosin (4.3% nightmare-free nights). Except dizziness, which was not regarded as particularly bothersome by the patient, doxazosin was well tolerated. It is concluded that doxazosin may be indicated as a pharmacological treatment for patients suffering from posttraumatic stress disorder–related nightmares.

## Keywords

$\alpha_1$ -adrenergic antagonist, doxazosin, nightmare disorder, treatment

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## Introduction

Nightmare disorder is characterized by episodes of extended, very frightening, and well-remembered dreams. Usually, nightmares involve threats to survival, security, or physical integrity. When the person awakens from a nightmare, he or she swiftly regains full consciousness and thus becomes oriented and alert. The dream experience, or the dream disturbance, which is a consequence of awakening from it, causes clinically significant distress or impairment in social, occupational, or other important areas of functioning. The latter is indicated by the patients reporting at least one of the following: sleep resistance, mood disturbance, cognitive impairments, negative impact on caregiver or family functioning, behavioral problems, daytime sleepiness, fatigue or low energy, impaired occupational or educational function, or impaired interpersonal/social function.<sup>1</sup> It has been argued that a distinction between idiopathic nightmares and posttraumatic stress disorder (PTSD)-related nightmares is warranted. PTSD-related nightmares seem, among others, to be characterized by more awakenings than idiopathic nightmares<sup>2</sup> and by higher sympathetic activation during rapid eye movement (REM) sleep than in normal controls.<sup>3</sup>

In regard of pharmacological treatment, the  $\alpha_1$ -adrenergic antagonist prazosin has in several randomized

controlled trials showed clinical effect for PTSD-related nightmares;<sup>4–6</sup> however, in a recent study with military veterans suffering from PTSD, prazosin did not improve posttraumatic stress symptoms, nightmares, and sleep problems in general compared to placebo.<sup>7</sup> A retrospective chart review concluded that prazosin is effective for pediatric PTSD-associated nightmares and sleep disturbances.<sup>8</sup> For adults, dosages are normally titrated up to 12 mg for women and 25 mg for men,<sup>5</sup> whereas the dosages for youth seem to vary between 1 and 15 mg.<sup>8</sup>  $\alpha_1$ -receptors are located in locus coeruleus, cerebral cortex, and limbic regions such as hippocampus and amygdala. It has been reported that  $\alpha_1$ -receptor stimulation disturbs REM sleep

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and increases non-REM sleep. Furthermore, stimulation of  $\alpha_1$ -receptors causes release of corticotropin-releasing hormone, which triggers the cortisol stress response.<sup>9</sup>

In a conditioning study, prazosin was shown not to affect threat conditioning, but augmented stimulus discrimination between safe and threatening stimuli during extinction and reextinction, hence prazosin may facilitate discrimination between the safe and threatening stimuli.<sup>10</sup> Prazosin crosses the blood–brain barrier, antagonizes the  $\alpha_1$ -receptors in the central nervous system (CNS) and by this blocks the stress responses by which prazosin improves sleep and reduces PTSD-related nightmares.<sup>9</sup> In some countries, including Norway, prazosin is however not available as a regular prescription drug. Other  $\alpha_1$ -adrenergic antagonists may, however, have similar therapeutic properties. In one uncontrolled study, the  $\alpha_1$ -adrenergic antagonist doxazosin, titrated up to 8 mg daily, was shown to be effective against nightmares.<sup>11</sup> This was also supported by a more recent case study.<sup>12</sup> In a crossover trial with eight patients suffering from PTSD, doxazosin was titrated from 4 to 16 mg daily over 12 days. On some PTSD-outcome measures, doxazosin improved PTSD symptoms, but not on a subscale assessing problematic dreams.<sup>13</sup> A chart review concluded, however, that doxazosin might improve nightmares associated with trauma as well as sleep parameters in general in patients with PTSD and borderline personality disorder.<sup>14</sup> Prazosin has a half-life of only 2–3 h and has thus to be taken twice daily, whereas doxazosin has a considerably longer half-life, approximately 22 h.<sup>15</sup> This implies that the effects of prazosin may subside during the night which may increase the risk of nightmares in the latter half of sleep in contrast to doxazosin.<sup>16</sup> Hence, more studies on doxazosin as a treatment for PTSD-related nightmares are warranted.

## Case

Here, we describe a diary-based case study of a 56-year-old woman strongly affected by PTSD-related nightmares. The nightmares were triggered by an incident where the patient during hospitalization became the victim of a grossly erroneous medical treatment as racemic adrenaline, which should be delivered by aerosol, instead was administered through a peripheral intravenous catheter. The patient got seizures, severe tachycardia, and hypertension. The black hair of a nurse bending over the patient during the incident became associated with an eagle, which appeared in subsequent dreams, attacking the patient. The patient experienced that sleeping following a nightmare became difficult. Furthermore, the nightmares caused tiredness/sleepiness, lack of ability to concentrate, nervousness during daytime, and acted as a reminder of the trauma. The patient also became afraid of sleeping in new contexts as this often provoked nightmares. The patient was not bothered with nightmares before the incident. All nightmares she experienced were related to the incident. The symptoms triggered by the incident made her fulfill the criteria for PTSD found in the ICD-10 Classification of

**Table 1.** Logistic regression analysis where time and dosage of doxazosin were regressed on nightmare occurrence (0 = nightmare present, 1 = nightmare absent).

Predictor	Crude		Adjusted	
	OR	95% CI	OR	95% CI
Day	1.01	1.00–1.01**	1.00	1.00–1.01
Doxazosin <sup>a</sup>				
4 mg	6.07	0.76–48.53	8.06	0.96–67.5
8 mg	27.10	3.58–205.31**	28.15	3.71–213.89**

OR: odds ratio; CI: confidence interval.

<sup>a</sup>0 mg doxazosin comprised the reference category.

\*\* $p < 0.01$ .

Mental and Behavioural Disorders.<sup>17</sup> The patient had been suffering from nightmares for 11 months before she started treatment with doxazosin in December 2012.

She kept a diary with information about dosage (0, 4, and 8 mg of doxazosin) and nightmare occurrence (occurred or not occurred) for 280 consecutive days. The dosage varied due to factors such as hospitalization and deliberate experimentation on behalf of the patient. The patient was instructed by her medical doctor to take doxazosin in doses up to 8 mg per day. The dosage varied between 4 and 8 mg (one or two tablets) due to dizziness as a side effect, typically lowering the dosage when dizziness became somewhat conspicuous. During periods of hospitalization, doxazosin was normally not administered.

A logistic regression analysis was conducted in which day was entered as a control variable in order to control for time as a confounding factor. The dosage of doxazosin was dummy coded and 0 mg of doxazosin constituted the reference category. Nightmare occurrence (0 = present, 1 = absent) comprised the dependent variable. In the crude analysis, the two predictors (day and dosage) were entered/analyzed separately, whereas in the adjusted analysis they were entered simultaneously. The result is considered significant when the 95% confidence interval does not include 1.00. In total, there were 23 days when the patient did not take any medication (0 mg doxazosin), 74 days when the patient took 4 mg of doxazosin, and 183 days when the patient took 8 mg of doxazosin. Of the 280 days, nightmares occurred on 162 nights and were absent on 118 nights. Cross-tabulation of dosage and nightmare frequency showed that only one of the 23 days (4.3%) without medication was nightmare free. Nightmare was absent in 16 of the 74 days (21.6%) with 4 mg of doxazosin, whereas nightmares was absent in 101 of the 183 days (55.2%) with 8 mg of doxazosin. The results are presented in Table 1. The adjusted model was statistically significant ( $\chi^2 = 45.7$ ,  $df = 3$ ,  $p < 0.001$ ) and explained between 15.1% (Cox and Snell  $R^2$ ) and 20.2% (Nagelkerke  $R^2$ ) of the variance in nightmare occurrence and correctly classified 62.5% of the nights. The results showed that doxazosin 8 mg had a better effect on nightmare occurrence than no medication. Doxazosin 4 mg had a near significantly better effect on

nightmare occurrence than no medication. Hypotension is a potential side effect of  $\alpha_1$ -adrenergic antagonists<sup>18</sup> and the patient experienced some dizziness in hot weather when taking 8 mg doxazosin and rising quickly from lying positions. The patient did, however, not regard this as bothersome. At one occasion when she had taken 8 mg of doxazosin, the patient fainted. Besides dizziness, no other side effects were noted by the patient. The patient went to regular check-ups of the blood pressure during the doxazosin treatment, and blood pressure was not abnormal at any point. Although a daily dose of 8 mg of doxazosin did not eliminate nightmares completely, the reduction in nightmare frequency was experienced as a clinical significant improvement by the patient.

## Discussion

This case study suggests that doxazosin seems to alleviate PTSD nightmares at least when taken in dosages of 8 mg or more. As this study suggests a dose-dependent effect, it is possible that higher doses would have produced even better outcome, and studies have shown that dosages up to 16 mg per day seem to be tolerated well.<sup>13</sup> This study lasted for 280 days and the effects of doxazosin did not seem to wear off by time, indicating no development of tolerance. It should be noted that no placebo was used in this study and that the patient partly experimented with different dosages by herself, hence the results may have been influenced by expectations on behalf of the patient. Still, as the study lasted for 280 days and consistently showed effects of 8 mg of doxazosin, it is concluded, in line with other studies,<sup>11,12,14</sup> that doxazosin may be indicated as a pharmacological treatment for patients suffering from nightmares. Doxazosin also seems to be well tolerated. We strongly recommend a large randomized controlled trial of the effectiveness of doxazosin against nightmares to be conducted. A comparative study between doxazosin and prazosin also seems warranted.

## Conclusion

A doxazosin dose of 8 mg seemed to alleviate PTSD-related nightmares, was well tolerated, and did not lead to tolerance during the 280-day study period.

## Author's note

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## Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

## Ethical approval

Our institutions do not require ethical approval for reporting individual cases or case series.

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## Informed consent

Verbal and written informed consent was obtained from the patient(s) for their anonymized information to be published in this article. The patient had completed college education and was not suffering from psychosis or any other delusional disorder. Thus, she was deemed to have the decisional capacity to provide informed consent.

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