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Evaluation of low dose prazosin for PTSD-associated nightmares in children and adolescents

Nancy Hudson, PharmD[1]; Steven Burghart, DPh, RPh, MBA, BCPP[2]; Jill Reynoldson, PharmD, BCPP, DPLA[3]; Dennis Grauer, MS, PhD[4]

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Abstract

Introduction: Knowledge about fundamental sleep disorders and dysregulation that occurs in children with PTSD is limited. Prazosin is an alpha-1 receptor antagonist often used off label for the treatment of PTSD-associated nightmares in adults; however, evaluation of its use in pediatrics and adolescents is limited. The primary objective of this study was to assess the impact of prazosin on nightmares associated with PTSD in this population. Secondary objectives included assessing side effects, changes in blood pressure, and 30-day readmission rates.

Methods: This was a retrospective, single-center chart review of inpatients diagnosed with PTSD nightmares from January 1, 2017, to July 31, 2019. Patients 4 to 18 years old with a PTSD diagnosis, experiencing nightmares, and initiating any dose of prazosin were assessed to determine efficacy and tolerance.

Results: Forty-two patients were evaluated to determine symptom improvement after initiation of prazosin for PTSD nightmares in children and adolescents. Of the 42 patients, 24 (57.1%) reported improvement in nightmares (average dose 1.05 mg). For secondary results, 38 (90.5%) patients continued prazosin at discharge, and 2 (5%) were readmitted within 30 days for reasons other than PTSD-associated nightmares. Thirty-four (81%) reported having no adverse effects to prazosin. There was no significant difference in systolic ($P = .1883$) or diastolic ($P = .2777$) blood pressure preinitiation and postinitiation of prazosin.

Discussion: Despite the limitations of this retrospective study, the data suggests that prazosin may be associated with an improvement in nightmares in children and adolescents with PTSD. Adverse events were rarely reported, and there was no significant change in blood pressure with initiation of prazosin.

Keywords: nightmares, children, adolescent, prazosin, PTSD

[1] (Corresponding author) PGY-1 Pharmacy Practice Resident, The University of Kansas Health System, Kansas City, Kansas, nhk99@mail.umkc.edu, ORCID: https://orcid.org/0000-0002-9628-0857; [2] Clinical Pharmacist, The University of Kansas Health System, Kansas City, Kansas, ORCID: https://orcid.org/0000-0001-8893-4171; [3] Pharmacy Manager, Psychiatry, The University of Kansas Health System, Kansas City, Kansas, ORCID: https://orcid.org/0000-0001-6209-8419; [4] Associate Professor, Vice Chair of Research, The University of Kansas School of Pharmacy, Lawrence, Kansas, ORCID: https://orcid.org/0000-0002-1490-0101

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Introduction

PTSD may occur in individuals who have witnessed or been exposed to, whether directly or indirectly, a shocking, scary, or dangerous event and has a lifetime prevalence of 6.8% in adults.[1] Symptoms of PTSD may include flashbacks, physiologic reactivity upon exposure to cues, diminished interest, irritable or aggressive behavior, and difficulty sleeping with or without nightmares. Nightmares related to PTSD are associated with increased frequency compared with non–trauma-related nightmares as well as severe insomnia and more frequent awakenings.[2,3] Despite increased awareness of PTSD nightmares

in adults, knowledge about fundamental sleep disorders and dysregulation that occur in children and adolescents with PTSD is limited. In pediatric PTSD populations, self-reported, guardian-reported, and clinician-administered questionnaires reveal higher reports of nightmares than in the average pediatric population.[4]

According to the National Institute of Mental Health,[5] the main treatments for adults with PTSD are psychotherapy, pharmacotherapy, or both. Although the most studied class of medication for treating PTSD is antidepressants, only minimal evidence suggests a benefit to adding SSRIs to trauma-focused, cognitive-behavioral therapy in children and adolescents.[6] Current evidence, therefore, supports an initial trial of evidence-supported, trauma-focused psychotherapy for most children with PTSD symptoms before adding medication. In specific PTSD symptoms, such as sleep problems and nightmares, medications other than antidepressants have been used.[5] Norepinephrine release may be correlated with the pathophysiology of PTSD as higher norepinephrine cerebrospinal fluid concentrations have been found in patients with PTSD and are associated with greater severity of PTSD symptoms.[7] This increased noradrenergic state in the central nervous system contributes to the disruption of normal rapid eye movement sleep, which, in turn, contributes to nightmares.[8] Therefore, an agent that blocks postsynaptic adrenergic receptors is a possible pharmacologic approach to the treatment of PTSD-associated nightmares. One such agent is prazosin, a lipid-soluble alpha-1 adrenergic receptor antagonist that crosses the blood-brain barrier and decreases the sympathetic outflow in the brain. Approved by the US FDA as an antihypertensive medication, prazosin was previously recommended in 2010 for the treatment of PTSD-associated nightmares in adults by the American Academy of Sleep Medicine with a level A recommendation (recommended, assessment supported by a substantial amount of high-quality level I or II evidence and/or based on a consensus of clinical judgement).[9] In 2018, the American Academy of Sleep downgraded the recommendation for prazosin due to a lack of evidence supporting its use in veterans with chronic PTSD; however, it remains a first-line option in adults due to perceived patient response.[10] Prazosin has not been well studied in treating nightmares associated with PTSD in children and adolescents, but several case reports and a retrospective chart review in 2017 show improvement in nightmares when doses of prazosin ranging from 1 to 15 mg/d were used.[11,12]

Based on current studies, awareness of prazosin for the treatment of PTSD-associated nightmares in adults is increasing; however, studies in children still remain limited.[13] The aim of this study was to retrospectively evaluate the use and effectiveness of low-dose prazosin in the treatment of PTSD-associated nightmares in children and adolescents.

Methods

This study was conducted at a stand-alone, 84-bed inpatient child and adolescent psychiatric facility within a large academic health system. Inclusion criteria were patients aged 4 to 18 with PTSD-associated nightmares who initiated treatment with prazosin from January 1, 2017, to July 31, 2019, after having engaged in evidence-based, trauma-focused psychotherapy per hospital protocol. Patients were excluded if they had previous use of prazosin for PTSD-associated nightmares or concomitant use of trazodone or cyproheptadine as the concomitant use of trazodone and prazosin can increase the risk of priapism and cyproheptadine is another treatment for nightmares. Patients were identified using an electronic health record workbench report based on administration of prazosin and/or diagnosis of PTSD defined by chart review and International Classification of Diseases code.

The primary objective was to determine any decrease in nightmares based on review of prescriber notes rather than a standardized scale. Secondary objectives were to evaluate side effects, determine changes in blood pressure postinitiation of prazosin, and assess 30-day readmission rates. Events were identified by provider notes via chart review.

Data collected included baseline demographic information, body mass index, comorbid psychiatric conditions, concurrent use of other psychiatric medications, length of stay, average number of days until initiation of prazosin, dosing, and information about continuation upon discharge.

As we did not have a comparator group, the primary and secondary results are described by descriptive statistics. Average blood pressures before and after initiation of prazosin were compared and analyzed using two-tailed, unpaired Student *t* tests. Results were considered statistically significant at $P < .05$ using a 95% confidence interval. IBM Statistical Product and Service Solutions Statistics (version 26) was utilized for data analysis.

Results

Two hundred three patients were identified for potential inclusion in the analysis. The primary reason for exclusion is prior use of prazosin at time of admission. Forty-two patients were included in the final analysis. Baseline characteristics, comorbid psychiatric conditions, and use of other psychiatric medications are reported in Table 1. The average age was 14.9 years; there were 35 (83%)

TABLE 1: Demographics of the patients included in the study[a]

Patient Characteristics	N = 42
Age at diagnosis, y, median (range)	14.88 (10-18)
Female, n (%)	35 (83)
Race, n	
White	32
Black or African American	3
Asian	1
Unknown	6
BMI, median (range)	26.1 (16.4-43.7)
Length of stay, d, median (range)	4.02 (2-7)
No. of d until prazosin started, median (range)	1.35 (1-6)
Prazosin continued at discharge, yes, n (%)	38 (91)
Prazosin starting dose, mg	
1	40
2	2
Comorbid psychiatric conditions	
Depression	39
Anxiety	24
Suicidal ideation	23
ADHD	15
Bulimia	4
Schizophrenia	2
OCD	2
Bipolar	1
Use of other psychiatric medications	
Fluoxetine	12
Sertraline	12
Escitalopram	7
Quetiapine	7
Aripiprazole	7
Lurasidone	6
Hydroxyzine	3
Citalopram	2
Risperidone	2
Venlafaxine	2
Lithium	2
Lamotrigine	1
Olanzapine	1
Duloxetine	1
Valproic Acid	1

[a]There were 203 patients initially; 161 patients excluded (160 had prior use of prazosin; 1 had prior use of trazodone).

female patients, and 32 (76%) were white. Of the 42 patients, 39 (93%) had a MDD diagnosis, 24 (57%) had a generalized anxiety disorder diagnosis, and 23 (55%) had suicidal ideation on admission. All study participants were on additional psychiatric medications, of which the top 2 were fluoxetine (n = 12, 29%) and sertraline (n = 12, 29%).

TABLE 2: Primary and secondary outcomes (N = 42)

Primary Outcomes	n (%)[a]
Reported decrease in nightmares	
Yes	24 (57)
No	5 (12)
Not recorded	13 (31)
Secondary Outcomes	
Adverse effects	
No side effects reported	34
Dizziness	1
Headache	1
Nausea	1
Not recorded at all	6
30-d readmission	
Yes	2 (5)

[a]Secondary outcomes do not show a percentage.

Patients stayed for an average of 4.02 days with an average of 1.35 days until the first dose of prazosin was initiated (average dose 1.05 mg). Thirty-eight (91%) patients were continued on prazosin at discharge.

Twenty-four (57%) patients reported a decrease in frequency of nightmares according to provider notes, 5 (12%) patients reported no change in frequency of nightmares, and 13 (31%) had no recorded outcome of medication response documented in the chart. For secondary outcomes, only 2 patients reported having side effects due to prazosin with 1 patient experiencing dizziness and headache and the other experiencing nausea. Documentation of no side effects to prazosin was reported in 34 (81%) patients. Six patients' notes showed no record of being asked about side effects related to prazosin. Two (5%) patients were readmitted within 30 days, but neither was for reasons related to PTSD-associated nightmares. Additionally, as prazosin is an approved hypertension medication, we assessed systolic and diastolic blood pressures preinitiation and postinitiation of prazosin and determined that there was no significant difference in systolic (119 ± 5.7 and 116.3 ± 13.5 mm Hg, respectively; $P = .1883$) or diastolic (68.5 ± 7.1 and 66.5 ± 9.5 mm Hg, respectively; $P = .2777$) blood pressure (Tables 2 and 3).

Discussion

This study evaluated low-dose prazosin for the treatment of PTSD nightmares in children and adolescents. Patients 4 to 18 years old diagnosed with PTSD according to the DSM-5 criteria who received evidence-based, trauma-

TABLE 3: Average blood pressure changes before and after initiation of prazosin

	Baseline, Average	SD	Post Prazosin, Average	SD	*T* test *P* Values
Systolic, mm Hg	119.3	5.7	116.3	13.5	.1883
Diastolic, mm Hg	68.5	7.1	66.5	9.5	.2777

focused psychotherapy were started on low-dose prazosin for treatment of nightmares.

The baseline characteristics show that the patients were predominantly female (83%) and white (76%). The patients stayed for an average of 4 days and started prazosin for PTSD nightmares an average of 1 day after admission. It is unclear from provider notes the exact time when the medication was deemed effective and whether or not a longer stay would change the outcome. We noted that prazosin was initiated at 1 or 2 mg nightly with 24 (57%) of patients recorded as seeing an improvement in their nightmare symptoms on this dosing and 38 (91%) patients continuing on prazosin at discharge. However, upon further investigation, we noted that 13 (31%) patients' provider notes did not mention nightmares at all beyond the admission note, which may be due to PTSD not being the primary reason for admission. Low-dose prazosin seems generally well tolerated in the first week of medication initiation for this patient population as 34 (81%) patients reported not experiencing any side effects, 1 patient reported having both dizziness and headache, and 1 patient reported having nausea. Prazosin did not seem to have a significant impact on this patient population's blood pressure after initiation, so it is likely that most patients do not need daily blood pressures at home; however, it should be noted that blood pressure readings were not conducted regularly throughout the day.

There were limitations to this study. The retrospective nature made data collection difficult as we relied on provider notes to indicate whether a patient experienced a decrease in nightmare frequency after the initiation of prazosin. Baseline trauma source was not documented regularly and, thus, not collected. Therefore, this important baseline characteristic is missing which, in real-world practice, may be associated with medication response. Due to a lack of a standardized method for the providers to document improvements, the timing of when nightmares improved was also not consistent. Some providers would document about nightmares daily, some would mention that the patient was no longer having nightmares on the discharge note, and others only mentioned nightmares at time of admission. A questionnaire may help standardize the questions that providers asked as well as the results recorded due to the subjective nature of this data. We also excluded patients that were currently on prazosin at admission, so we were unable to capture information on dose increases or discontinuations due to ineffectiveness. We tried to capture long-term effectiveness with 30-day readmission rates; however, without outpatient follow-up, we were unable to confirm if patients were able to continue this medication or determine if they sought care at another facility. Additionally, hospital length of stay was short, and therefore, dose titrations were uncommon, so dose at discharge was usually the same as the starting dose, which may be not reflective of current practice. Blood pressure readings were not conducted regularly throughout the day, and as this was a retrospective chart review, we could not assess how the blood pressures were taken. As these patients were not on continuous telemetry and prazosin was given at bedtime, we did not intend to track and report immediate changes in blood pressure; however, future studies would benefit from looking at significant individual blood pressure changes as an average may blunt any blood pressure outliers. With prazosin's antihypertensive peak effect at 2 to 4 hours after administration, with a duration of 10 to 24 hours, it may be more beneficial to conduct blood pressure readings several hours after a dose.[14] Prazosin also has a known side effect of orthostasis, but that was not evaluated in this study. Because we did not have a comparator group, there was no assurance that the outcomes studied were due to the treatment rather than other factors.

Conclusion

Prazosin may be safely initiated for treatment of nightmares in children and adolescents with PTSD. In this study, it was well tolerated with few side effects reported. As this medication can also be used to treat hypertension, our data show there was no significant difference in blood pressure changes postinitiation of prazosin. A prospective, randomized control trial of prazosin in this population is warranted.

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