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Comparison of alpha-2 agonist versus alpha-1 antagonist for post-traumatic stress disorder–associated nightmares in pediatric patients

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Abstract

Introduction: Posttraumatic stress disorder (PTSD) in children and adolescents has a high prevalence of accompanying sleep disturbances. Currently, pediatric treatment of PTSD-related nightmares is extrapolated from adult studies. This study aims to determine the effectiveness and safety of clonidine and guanfacine compared with prazosin for the treatment of PTSD-related nightmares.

Methods: This was a retrospective, single-center, medical record review of patients 5 to 17 years old admitted to an inpatient psychiatric unit from January 2015 to September 2021. Patients with a new initiation of an alpha-2 agonist (clonidine or guanfacine) or an alpha-1 antagonist (prazosin) with a diagnosis of PTSD, other trauma- or stressor-related disorder or unspecified anxiety disorder were included. The primary endpoint was the percentage of patients with a decrease in the frequency of nightmares.

Results: A total of 59 patients were included in the study: 37 in the alpha-2 agonist group and 22 in the alpha-1 antagonist group. There was no statistically significant difference in reduction of nightmares with both groups having a high percentage of patients showing response (alpha-2 agonist: 91.9%, alpha-1 antagonist: 86.4%). Time to decrease in nightmares was comparable between groups with a relatively quick onset. Within the alpha-2 agonist group, clonidine (1.59 ± 1.06 days) compared with guanfacine (3.18 ± 1.74 days) had a statistically significant faster time to reduction in nightmares ($p = .005$).

Discussion: Both pharmacologic classes of medications were effective treatment options for pediatric PTSD-associated nightmares with a low incidence of adverse effects. There was a quick time to onset seen with all agents.

Keywords: pediatric, posttraumatic stress disorder, PTSD, clonidine, guanfacine, prazosin, nightmares

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Introduction

The National Institute of Mental Health reports a lifetime prevalence of posttraumatic stress disorder (PTSD) to be approximately 5% in adolescents with the prevalence higher for females compared to males.[1] PTSD consists of symptoms that can be organized into 4 clusters: negative alterations in cognition, avoidance of stimuli, alterations in arousal and reactivity, and intrusion symptoms. Intrusion symptoms can consist of flashbacks, recurrent nightmares, dissociative reactions, intrusive memories, and psychological distress upon exposure to cues or triggers related to the

traumatic event.[2] Several studies assess the occurrence of sleep disturbances in children with PTSD and compare the prevalence to non–trauma exposed children.[3,4] Nightmares are a part of the normal developmental process in children and adolescents; a longitudinal study conducted by Schredl and colleagues reported nightmare incidence in children to be between 2.5% and 3.5%.[5] The rate of nightmares and sleep disturbances in adolescents exposed to trauma is significant with studies reporting prevalence rates up to 50% to 80%.[4]

Studies on the pathophysiology of PTSD suggest that noradrenergic hyperactivity in the central nervous system is linked to intrusion symptoms such as nightmares. Therefore, it is postulated that medications that can reduce this noradrenergic hyperactivity can decrease intrusive symptoms.[6] Alpha-2 agonists such as clonidine and guanfacine work centrally and reduce norepinephrine release, whereas alpha-1 antagonists such as prazosin reduce noradrenergic hyperactivity by blocking postsynaptic norepinephrine receptors. Both pharmacologic classes have been used to reduce PTSD-related nightmares.

First line pharmacologic treatment of PTSD consists of using a selective serotonin reuptake inhibitor (SSRI).[7] However, pediatric treatment of PTSD-related nightmares is extrapolated from adult studies, and there is no guidance indicating preferred pharmacologic treatment options in children and adolescents. There are small studies, case reports, and case series analyzing individual alpha-2 agonist and alpha-1 antagonist efficacy in pediatric patients. However, to our knowledge, there are no studies directly comparing the 2 classes of medications.

Methods

Participants

This was a single-center, retrospective medical record review approved by the Virginia Commonwealth University (VCU) institutional review board and the VCU Children's Hospital protocol review and oversight committee. Patients aged 5 to 17 years old admitted inpatient for psychiatric management to the Children's Hospital of Richmond Virginia Treatment Center for Children at VCU between January 1, 2015, and September 30, 2021, were included in the study. Additionally, patients had to have a diagnosis of PTSD, other trauma- or stressor-related disorder, or unspecified anxiety disorder and be medication naïve to an alpha-2 agonist (guanfacine or clonidine) or alpha-1 antagonist (prazosin) during the admission. To be included in the study, patients had to have nightmares at baseline related to their diagnosis. Patients with a diagnosis of attention-deficit/hyperactivity disorder (ADHD) were excluded from the study to account for any possible treatment overlap with ADHD. Pregnancy and use of one of the 3 agents at time of admission were additional exclusion criteria. However, patients could be eligible for inclusion if they had a minimum of a 1-week washout period from their previous agent. Once this washout period was complete, they could be initiated on any alpha-2 agonist or alpha-1 antagonist even if previously prescribed the medication.

The objective of this study was to evaluate the safety and effectiveness of alpha-2 agonists compared to an alpha-1 antagonist for the treatment of PTSD-associated nightmares in pediatric patients. The primary outcome was a decrease in the frequency of nightmares defined by provider or therapist documentation on 2 consecutive days of patient-reported improvement in nightmares. Discussion of nightmares was a part of daily clinical rounds; documentation was based upon patient-reported reduction in number of nightmares and provider assessment of the patient. Secondary outcomes included time to decrease in nightmares, clinically significant hypotension or bradycardia, decrease in frequency of daytime flashbacks and/or intrusive memories, and 30-day readmission rates for any psychiatric cause. An additional secondary objective was establishing pediatric dosing of these medications due to lack of recommendations in the literature. Dosing range was based upon minimum and maximum doses provided to patients during the duration of the study.

Time to decrease in nightmares was measured by the first documented day noting improvement in nightmares, confirmed by assessing this improvement for 2 consecutive days. Clinically significant hypotension or bradycardia were defined as documentation of low heart rate (<50 beats per minute) or blood pressure ($<90/50$ mmHg) in addition to documentation of dizziness, fainting, blurred vision, or falls. Reduction in flashbacks and/or intrusive memories was determined based upon addition of daytime dose of alpha-2 agonist or alpha-1 antagonist and documented note from provider or therapist stating patient has seen improvement.

Data Collection

Baseline demographics collected included age, sex, race, diagnosis, comorbidities, concomitant medications, previous use of alpha-2 agonist, and/or previous use of alpha-1 antagonist.

Statistical Methods

Continuous variables were analyzed utilizing the Student *t*-test and were reported as the mean with the standard deviation. Categorical variables were analyzed using the chi-square test and Fisher exact. All data analysis was performed

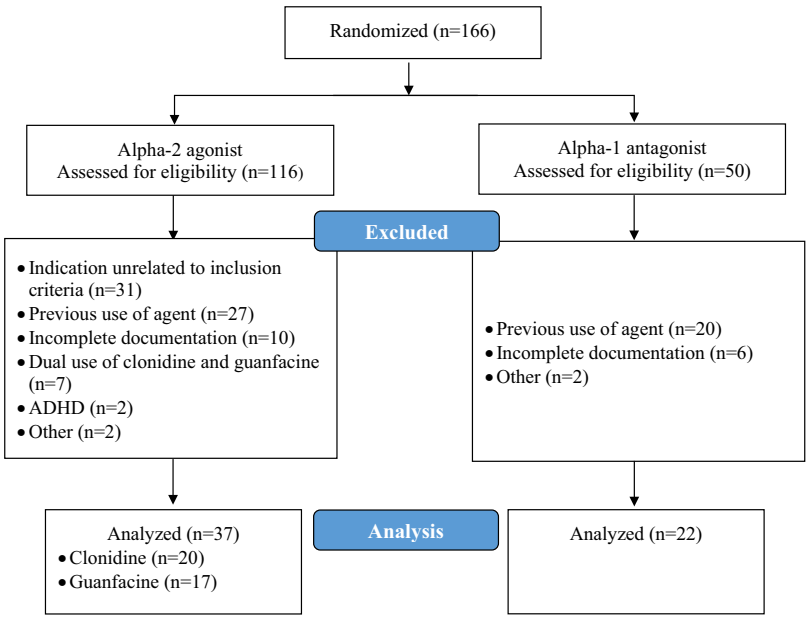

FIGURE: **CONSORT flow diagram**

utilizing SAS JMP version 16.1, and a two-sided *p*-value of less than 0.05 was considered statistically significant.

Results

Overall, 166 patients were reviewed for eligibility and 59 were included in the analysis. The most common reasons for exclusion were admission to the hospital already taking study medications and indication for use other than PTSD-related nightmares. The complete exclusion reasons are reported in the Figure. Of the 59 patients analyzed, most were approximately 14 to 15 years old. Most patients in both groups were female (alpha-2 agonist 83.8%, alpha-1 antagonist 86.4%) and Caucasian (alpha-2 agonist 51.4%, alpha-1 antagonist 54.5%). The most common diagnosis for inclusion was PTSD in both groups (alpha-2 agonist 62.2%, alpha-1 antagonist 72.7%). Patients had a high likelihood of having comorbid depression (alpha-2 agonist 81.1%, alpha-1 antagonist 68.2%). The patients in the alpha-1 antagonist group had a higher incidence of comorbid anxiety (59.14%) compared with the alpha-2 agonist group (27%) ($p = .015$). The most common concomitant medication patients were on was an SSRI with 73% of patients on an SSRI in the alpha-2 agonist group and 72.7% of patients in the alpha-1 antagonist group. The full baseline characteristics are listed in Table 1. Patients were only initiated on the immediate release formulation of clonidine and guanfacine during the study period for the indications assessed in this study.

For the primary endpoint, there was no statistically significant difference in frequency of nightmares with 91.9% of patients having a reduction in nightmares for the alpha-2 agonist group and 86.4% in the alpha-1 antagonist group ($p = .661$). For the secondary outcomes, there was no statistically significant difference between the groups (Table 2). Reduction was seen in both groups regarding frequency of flashbacks and/or intrusive thoughts with the alpha-2 agonist group at 40.5% compared with 27.3% in the alpha-1 antagonist group; however, this was not statistically significant ($p = .303$). The incidence of clinically significant hypotension for the alpha-2 agonist was 8.1% compared with 4.5% for the alpha-1 antagonist ($p = 1$). On average, it took 2.38 days to decrease nightmares in the alpha-2 agonist group and 2.11 days in the alpha-1 antagonist group ($p = .524$). When analyzed by individual agent, there was no difference between prazosin (2.01 days) and guanfacine (3.18 days) or prazosin and clonidine (1.59 days) for time to decrease in nightmares. However, when assessing clonidine compared with guanfacine, there was a statistically significant difference ($p = .005$) with clonidine having a faster time to reduction in nightmares. There was no statistical significance in 30-day readmission rates between the groups (alpha-2 agonist: 8.1%, alpha-1 antagonist: 0%; $p = .286$). Dosing characterization for each agent are reported in Table 3.

Discussion

This retrospective medical record review assessed the effectiveness of alpha-2 agonists compared with an alpha-1 antagonist in the treatment of PTSD-related nightmares; our findings suggest there is no significant difference between the 2 groups regarding reduction in frequency of PTSD-related nightmares. These results suggest that both pharmacologic classes are

TABLE 1: Baseline demographics

Characteristic	Alpha-2 Agonist ($n = 37$)	Alpha-1 Antagonist ($n = 22$)	*P*-value
Age in Years, Mean ± SD	14.27 ± 2.15	15.14 ± 1.52	.104
Female Sex, *n* (%)	31 (83.8)	19 (86.4)	.789
Race, *n* (%)			
Caucasian	19 (51.4)	12 (54.5)	.812
African American	11 (29.7)	5 (22.7)	.559
Other	6 (16.2)	5 (22.7)	.534
Diagnosis, *n* (%)			.407
PTSD	23 (62.2)	16 (72.7)	
Trauma- or Stressor-Related Disorder	14 (37.8)	6 (59.1)	
Comorbidities, *n* (%)			
Depression	30 (81.1)	15 (68.2)	.26
Anxiety	10 (27)	13 (59.1)	.015
Other	2 (5.4)	0	.267
Concomitant meds, *n* (%)			
SSRI	27 (73)	16 (72.7)	.983
SNRI	2 (5.4)	3 (13.6)	.272
SGA	5 (13.5)	1 (4.5)	.27
Previous use of Alpha Agonist, *n* (%)	3 (8.1)	2 (9.1)	1
Previous use of Alpha Antagonist, *n* (%)	0	2 (9.1)	.135

SGA = second-generation antipsychotic; SNRI = serotonin and norepinephrine reuptake inhibitor; SSRI = selective serotonin reuptake inhibitor.

effective treatment options as the incidence of nightmare reduction was reported to be greater than 80% in both groups.

Overall, both alpha-2 agonists and alpha-1 antagonists showed a quick onset of action averaging approximately 2 to 2.5 days. This information suggests that either pharmacologic class is a possible treatment option that can be utilized for rapid symptom management of PTSD-related nightmares. Additionally, when analyzing the time to onset by agent, the alpha-2 agonist clonidine had a statistically significant quicker time to onset in comparison with guanfacine. This could possibly be because only 1 patient initiated on clonidine was up-titrated past the initial dose, whereas those who were initiated on guanfacine had higher instance of dose titration before an effect was seen.

Regarding reduction in flashbacks and/or intrusive memories, there was no statistically significant difference between groups. From a safety perspective, there were no incidences of clinically significant bradycardia and minimal incidences of clinically significant hypotension. For 1 of the incidences of clinically significant hypotension, the patient had previously trialed an alpha-2 agonist, guanfacine, and it was discontinued due to hypotension. This was the second trial of the same agent, and the patient experienced hypotension with the second trial.

Patients were started and maintained on relatively low doses in both pharmacologic classes. For most patients, the dose was not increased beyond the initial dose. Once patients reported an initial improvement in their nightmares, most providers did not titrate the dose to assess if there would be further improvement with higher doses. Of the 6 patients in this study who did not note any improvement in nightmares, 3 of them were started on an initial dose of the medication class and were not titrated prior to discontinuing the medication. Two of the patients were titrated up only once prior to discontinuing the medication, and the last patient was unable to tolerate the titration due to dizziness and was discontinued. There would be value in additional studies assessing effectiveness in patients titrated further on their alpha-2 agonist or alpha-1

TABLE 2: Secondary outcomes

	Alpha-2 Agonist ($n = 37$)	Alpha-1 Antagonist ($n = 22$)	*P*-value
Time to Reduction in Nightmares (Days, Average), SD	2.38 ± 1.63	2.11 ± 1.24	.524
Decrease in Frequency of Flashbacks and/or Intrusive Thoughts, *n* (%)	15 (40.5)	6 (27.3)	.303
Clinically Significant Hypotension, *n* (%)	3 (8.1)	1 (4.5)	1
30-Day Readmission Rate, *n* (%)	3 (8.1)	0	.286

TABLE 3: Dosing characterization

	Mean Initial Dose (Range)	Mean Final Dose (Range)
Prazosin	1.1 mg (1–2 mg)	1.53 mg (1–4 mg)
Guanfacine	0.82 mg (0.5–1 mg)	1.19 mg (0.5–2 mg)
Clonidine	0.09 mg (0.05–0.1 mg)	0.1 mg (0.05–0.2 mg)

antagonist. The dosing ranges discussed in this paper can assist in determining initial dosing and when response can begin to be seen.

For patients with PTSD, the first line treatment is trauma-focused psychotherapy; however, when patients are unable to engage in any form of psychotherapy or symptoms are severe, pharmacotherapy can be considered. Currently, the FDA treatment options for PTSD include fluoxetine, paroxetine, sertraline, and venlafaxine. Based upon our study, if pediatric patients are experiencing distressing nightmares, an alpha-2 agonist or alpha-1 antagonist can be considered as a symptom-management strategy in addition to a first line agent such as an SSRI.

There are several limitations to this study. One significant limitation was provider selection bias. During our data collection, it was evident that certain providers preferred a pharmacologic class, and those agents were more likely to be given to their patients. Prior to the study, the outcomes of interest were well-defined to ensure consistency in data collection. However, the lack of an objective scale or questionnaire to assess clinical efficacy was a limitation. Due to this, the primary outcome could have been either a decrease in the number of nightmares that occurred each night or a decrease in nighttime awakening from nightmares. Other limitations include incomplete documentation, the small sample size, placebo effect, and the retrospective single center design of the study.

Our study is contributing to the limited body of literature evaluating pharmacotherapy for the treatment of PTSD-related nightmares in pediatric patients. Additionally, to our knowledge, there are currently no studies evaluating the efficacy of alpha-2 agonists compared with alpha-1 antagonists for PTSD-related nightmares.

Conclusion

The primary outcome showed no statistically significant difference between medication classes in reduction of PTSD-related nightmares. Both classes were effective in managing nightmares, had a quick onset of action, and overall were well-tolerated. Within the alpha-2 agonist class, it appears clonidine had a quicker onset of action in comparison with guanfacine; however, both options were equally effective. Future studies should be conducted with a larger sample size to confirm the results of this study.

References

1. National Institute of Mental Health. Post-traumatic stress disorder [cited 2022 Jun 13]. Available from: https://www.nimh.nih.gov/health/statistics/post-traumatic-stress-disorder-ptsd
2. American Psychiatric Association. Trauma- and Stressor-Related Disorders. In: Diagnostic and Statistical Manual of Mental Disorders, 5th ed. 2022.
3. Secrist ME, John SG, Harper SL, Conners Edge NA, Sigel BA, Sievers C, et al. Nightmares in treatment-seeking youth: the role of cumulative trauma exposure. J Child Adolesc Trauma. 2019 Jun 18;13(2):249-56. DOI: 10.1007/s40653-019-00268-y
4. Kovachy B, O'Hara R, Hawkins N, Gershon A, Primeau MM, Madej J, et al. Sleep disturbance in pediatric PTSD: current findings and future directions. J Clin Sleep Med. 2013 May 15;9(5):501-10. DOI: 10.5664/jcsm.2678
5. Schredl M, Fricke-Oerkermann L, Mitschke A, Wiater A, Lehmkuhl G. Longitudinal study of nightmares in children: stability and effect of emotional symptoms. Child Psychiatry Hum Dev. 2009 Sep;40(3):439-49. DOI: 10.1007/s10578-009-0136-y
6. Strawn JR, Geracioti TD Jr. Noradrenergic dysfunction and the psychopharmacology of posttraumatic stress disorder. Depress Anxiety. 2008;25(3):260-71. DOI: 10.1002/da.20292
7. Cohen JA, Bukstein O, Walter H, Benson SR, Chrisman A, Farchione TR, et al. AACAP work group on quality issues: practice parameter for the assessment and treatment of children and adolescents with posttraumatic stress disorder. J Am Acad Child Adolesc Psychiatry. 2010 Apr;49(4):414-30. PMID: 20410735