Prazosin in Children and Adolescents With Posttraumatic Stress Disorder Who Have Nightmares

A Systematic Review

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Abstract:

Background: The aim of this systematic review was to identify published articles that evaluated the use of prazosin for treating nightmares in children and adolescents who have posttraumatic stress disorder (PTSD).

Procedures: A literature search was conducted of PubMed, MEDLINE, EMBASE, Cochrane Collaboration, and PsycINFO databases for published articles in any language that evaluated the use of prazosin for treating nightmares in the context of PTSD in children and adolescents using the following key words: PTSD, nightmares, prazosin, children, adolescents, trauma, and sleep.

Results: A total of 9 published articles related to the use of prazosin for treatment of nightmares in PTSD in children and adolescents were identified. Six of the 9 articles that met our inclusion criteria were case reports. All of these 6 case reports showed marked improvement in nightmares when prazosin was used, although at a generally lower dose when compared with its use in adults, with dosing ranging from 1 to 4 mg/d.

Conclusions: Prazosin has shown promising outcomes in treating nightmares associated with PTSD in children and adolescents, although this has not been well studied. Future placebo-controlled trials are needed to assess the efficacy and safety of prazosin in treating PTSD-related nightmares in children and adolescents.

Key Words: adolescents, children, nightmares, prazosin, PTSD, sleep

(*J Clin Psychopharmacol* 2017;37: 84–88)

Posttraumatic stress disorder (PTSD) is a pathologic response to a traumatic event characterized by 4 clusters of symptoms according to the *Diagnostic and Statistical Manual of Mental Disorders* (*DSM*): intrusive symptoms (criterion B), avoidance symptoms (criterion C), negative alterations in cognition and mood (criterion D), and marked alterations in arousal and reactivity (criterion E). These symptoms must last for more than 1 month. If the symptoms do not manifest until at least 6 months after exposure to traumatic event, then a specifier of PTSD with delayed onset ensues.[1]

In contrast to adult PTSD, symptoms of distress following exposure to a traumatic event can vary in exposed children and adolescents. Factors influencing reaction to a traumatic event include the child's age, gender, proximity to the traumatic event, type of trauma, and previous history of trauma or psychiatric history; chronicity of the traumatic event; and presence of family, as well as social support. Traumatic stress symptoms of hyperarousal may include aggression, irritability, temper outbursts, reckless behavior, and sleep disturbance. Many of these symptoms arise because of prefrontal cortex (PFC) dysfunction.[2]

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Received June 29, 2016; accepted after revision November 1, 2016.
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ISSN: 0271-0749
DOI: 10.1097/JCP.0000000000000638

We focus on sleep disturbance as an important aspect of PTSD. In comparison to control subjects, patients with PTSD report much higher incidence of nightmares and insomnia. One study found that 70% to 91% of adults with PTSD have sleep disturbance. Increased frequency of sleep disturbance has also been reported in children and adolescents with PTSD, most of which is either self-reported or parent reported, with incidence as high as 77.1% following 1 month after exposure to a traumatic event.[3] Extremely distressing and disturbing nightmares not only can have a profound negative effect on an individual's sleep, but also can affect mental and physical health and quality of life and have negative impact on social and emotional functioning and overall sense of well-being of an individual.

There is recent evidence that suggests a role of norepinephrine (NE) in the pathophysiology of PTSD. Norepinephrine has been found in higher concentration in the cerebrospinal fluid of patients with PTSD.[4,5]

Prazosin is a lipid-soluble α1 adrenergic receptor antagonist and is the only available drug in this class that can cross blood-brain barrier, thereby decreasing sympathetic flow in the brain. It has been approved for the treatment of hypertension by the US Food and Drug Administration; however, it is also used off label for treatment of PTSD-associated nightmares, with some randomized controlled trial (RCT) studies conducted in adults showing that its use is more effective than placebo in the treatment of PTSD-associated nightmares.[5] There have also been some case reports with promising effect in its use for treatment of PTSD-associated nightmares in children and adolescents.[4,6–10]

Symptoms of PTSD have shown to improve significantly with treatment of associated sleep disorder. As there is a high rate of sleep disturbance in patients with PTSD and limited studies assessing treatment of sleep disorders in children and adolescents with nightmares, we conducted this review with the main objective of increasing awareness and recommending further research for sleep-related disorders in PTSD, as well as treatment of these disorders, in children and adolescents to reduce associated morbidity and mortality in this population of patients.

METHODS

A systematic review was conducted in accordance with guidance of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) (Fig. 1).[11]

The purpose of this review was to evaluate the data on use of prazosin in children and adolescents with PTSD-associated nightmares.

We conducted an extensive literature search on PubMed, MEDLINE, EMBASE, Cochrane, and PsycINFO collaborative databases through December 31, 2015, for published articles (case reports, systematic review, RCT) in any language. Keywords were as follows: trauma, PTSD, RCT, prazosin, children, adolescent, sleep disorder, insomnia, and parasomnia. We also reviewed the bibliographic database of published articles for additional studies.

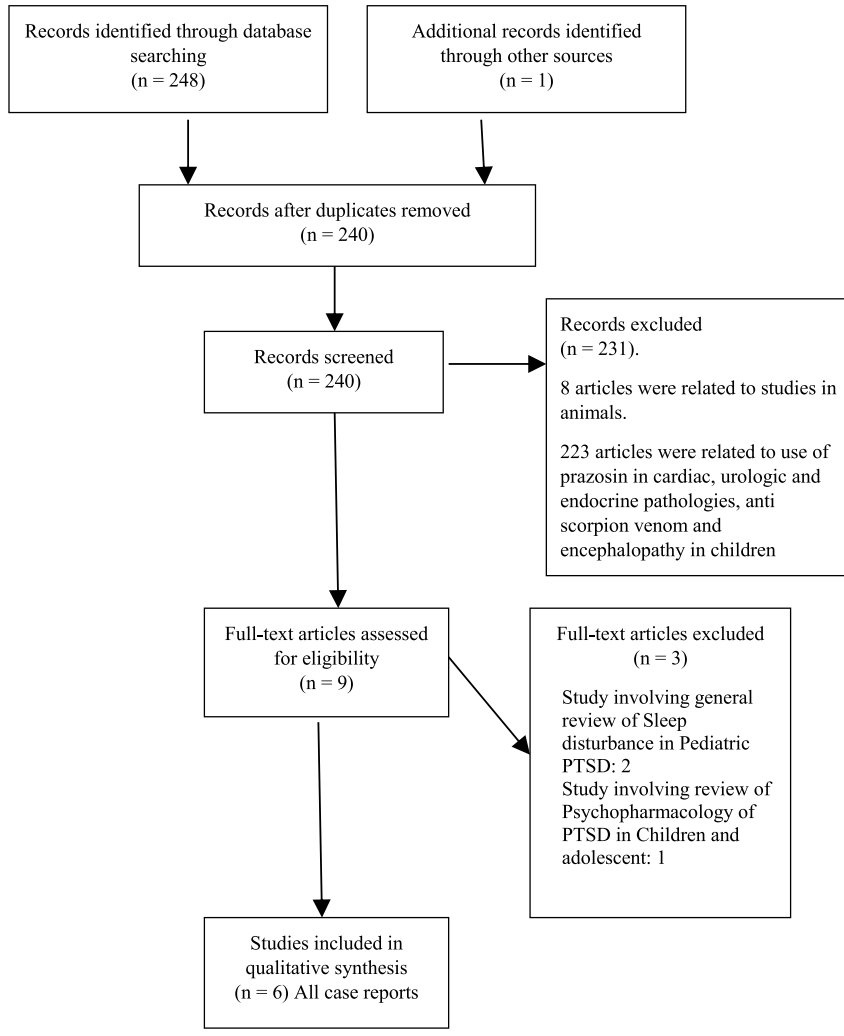

FIGURE 1. PRISMA flow diagram.

Inclusion criteria were any clinical trials, systematic reviews, and case reports for use of prazosin in PTSD-related nightmares in children and adolescents involving only human subjects that were published in English-language journals or had official English translation, although the initial search was not restricted by language.

The abstract and full-text articles from the citation obtained via the search of the database were reviewed by the 3 authors, A.A., R.R.T., and R.M. The decision on which studies to be included or excluded for the final analysis was done after a review of the full-text article by all the authors. Disagreement between the authors was resolved by a consensus; the quality of included studies was assessed using the criteria developed by the Center for Evidence-Based Medicine.[12]

RESULTS

Systematic review of our literature search identified 240 articles after duplicates were removed. Nine of them were assessed for eligibility, and only 6 met our inclusion criteria, which evaluated the use of prazosin in children and adolescents for treatment of nightmares associated with PTSD.

All the 6 published full-text articles were case reports. The ages of participants in these articles varied from 7 to 16 years. The duration of treatment exposure and follow-up varied from 4 weeks to 11 months.

In the earliest case report identified by this review, Brkanac et al[9] in 2003 reported a case of a 15-year-old girl with history of parental neglect and physical and sexual abuse leading to her being placed in foster care. She was admitted in a long-term psychiatric facility for treatment; she reported difficulty falling asleep, frequent awakening due to nightmares (4 times a week), increased arousal, irritability, impulsivity, occasional panic attacks, and dysthymia and received a diagnosis of PTSD. Her medication trial included nefazodone 200 mg, trazodone 50 mg, zolpidem 5 mg, and mirtazapine 45 mg, all at bedtime with no reported improvement in her symptoms. These medications were discontinued during her admission, and prazosin 1 mg at bedtime was started. She was also involved in individual and group therapies. Prazosin was increased to 4 mg (nightly at bedtime [qhs]) in 10 days and 4 weeks after prazosin was started. She reported improved sleep and no nightmares. Over the subsequent 2 months, she continued to have improved sleep with no nightmares, and global clinical improvement was also noted.

Strawn et al[6,10] identified 2 cases; the first[6] in 2009 was a case of a 16-year-old girl with acute PTSD following direct experience with armed robbery. She had a Clinician-Administered PTSD scale score of 67 (re-experiencing, 20; avoidant, 18; hyperarousal, 29) and severe nightmares. She was initiated on 1 mg prazosin qhs with increase to 2 mg qhs after 1 week. Her Clinician-Administered PTSD scale score decreased to 40 (re-experiencing, 6; avoidant, 20; hyperarousal, 14) after 1 month of treatment, and patient reported resolution of nightmares, as well as attenuation of her hyperarousal symptoms. The second reported case[10] was in 2011, that of a 7-year-old boy who had attention-deficit/hyperactivity disorder (ADHD), combined type, and PTSD (diagnosed per *DSM* criteria) that occurred as a result of a sexual assault. He had trials of melatonin 3 mg qhs and supportive psychotherapy, which were discontinued. He was started on extended-release dexmethylphenidate 5 mg every morning for his ADHD and prazosin 1 mg qhs for his PTSD symptoms. He reported cessation of nightmares within 1 month of treatment and subsequent reduced hyperarousal and gradually improved avoidant symptoms over the course of 10-month treatment, although there was a brief return of these symptoms for 4 to 5 days because of lapse in medication administration and subsequent disappearance of symptoms when family resumed prazosin 1 mg qhs.

In 2009, Fraleigh et al[7] reported a case of a 16-year-old boy with history of conduct disorder who was evaluated at a juvenile detention facility. He witnessed a friend's violent shooting and his cellmate's attempt to hang himself and received a diagnosis of PTSD. The case report does not mention how he met the criteria for PTSD. Prazosin was started at 1 mg qhs for treatment of trauma-related nightmares with increase to 1.5 mg qhs after several weeks. During 1½months of treatment on 1.5 mg qhs, his frequency of nightmares reduced from 7 to 0 per week. He reported nightmares again 5 times per week following discontinuation due to unknown reasons. He was restarted on the same dose, and after 1 month, he reported improved sleep with no nightmares.

Oluwabusi et al[8] in 2012 reported 2 cases, both females (15 and 16 years old) with history of sexual abuse and development of PTSD symptoms including hypervigilance, nightmares, insomnia, being easily startled, and hyperarousal symptoms. The 15-year-old also had diagnoses of mood disorder not otherwise specified and learning disability. She was started on sertraline, whereas the 16-year-old was given bupropion and trazodone. In both cases, cognitive behavioral therapy was also done. Both reported improvement of symptoms of PTSD with the exception of persistent insomnia and nightmares. Trazodone was discontinued in the 16-year-old, and prazosin was started at 1 mg qhs with titration to 1 mg in the morning and 2 mg qhs. The 15-year-old was also initiated on prazosin 1 mg qhs with subsequent titration to 3 mg qhs. They both reported improvement in nightmares after 2 weeks.

The most recent case report identified in our review is that of Racin et al[4] in 2014. They reported a case of a 10-year-old boy with a history of ADHD and significant childhood trauma (neglect, physical and emotional abuse, exposure to sexual content by biological mother) who was admitted for aggressive behavior and suicidal ideation. Prior to admission, he was prescribed guanfacine 1 mg in the morning and 0.5 mg in the afternoon and amphetamine mixed salts extended release 5 mg daily. Upon admission, he met the *DSM* criteria for PTSD, which included symptoms of being easily startled, nightmares, hypervigilance, and daily flashbacks of traumatic events. His medications were stopped, and he was initiated on prazosin 1 mg at 3 PM daily and titrated to 1 mg 3 times daily with subsequent improvement in his nightmares, intrusive symptoms, and poor impulse control and anger. He was also started on fluoxetine 10 mg daily and osmotic (controlled) release oral (delivery) system methylphenidate 18 mg daily, and he received daily supportive and weekly family therapy. At discharge, he had overall improvement in his symptoms. At 6 months' follow-up, frequency of his prazosin had been changed; he reported nightmares, and prazosin was reinitiated and increased to 2 mg qhs with subsequent relief of nightmares.

All of the 6 case reports showed marked improvement in nightmares, as well as hyperarousal and intrusive symptoms of PTSD when prazosin was used, although at a generally lower dose when compared with its use in adults. Three of the case reports reported an increase in intensity and frequency of nightmares following discontinuation of prazosin in children and adolescents with PTSD-associated nightmares who had been previously treated with prazosin and had reported remission of these nightmares.[4,7,8]

Prazosin was well tolerated in 5 of the 6 case reports, with the exception of one who reported increased weight gain and body mass index when patient was followed up over the course of 11 months' treatment (Table 1).[7]

DISCUSSION

One of the objectives of this systematic review was to identify evidence for the use of prazosin in the treatment PTSD-related nightmares in children and adolescents.

During exposure to stress, there has been extensive evidence suggesting elevated noradrenergic (NE) responsiveness, in addition to changes in the PFC area of the brain with postmortem evidence showing consistent signs of PFC dysfunction in patients with PTSD. Many of the intrusive and hyperarousal symptoms including nightmares arise from this dysfunction.[2,6]

The PFC can regulate our state of arousal through projections to the NE system, where it can inhibit locus ceruleus from firing, thereby reducing the stress response. Also, there is high level of noradrenergic activity during rapid eye movement sleep stage when compared with control.[8]

The hypothalamic-pituitary-adrenal axis is also believed to play a role in the neurobiology and neuroendocrine response to stress. In PTSD, there are increased glucocorticoid receptors, strong negative feedback, and hypersuppression of the dexamethasone suppression test. There is subsequent adrenergic modification leading to exaggerated increase in cardiovascular response in relation to the hyperarousal and intrusive symptoms. This is all manifested again by increases in urine, plasma, and cerebrospinal fluid catecholamines.[8]

Hence, it is prudent to use medications such as a centrally acting $\alpha 1$ receptor antagonist (prazosin) with pharmacologic action of inhibiting the actions of the sympathetic nervous system, ultimately leading to reduction of nightmares and rapidly improving PTSD symptoms via its inhibitory action on NE release.

Severity of nightmares and other sleep disturbances increases with severity of the traumatic event, as well as PTSD symptoms. Although the most extensively used method for measuring nightmares in children with PTSD is subjective (patient reported, parent reported, and clinician interview), data gathered suggest that the prevalence of PTSD is markedly relevant, with some studies reporting prevalence as high as 50% to 80%.[3] Kovachy et al[3] assessed sleep disturbance in pediatric PTSD, and they reported variability in reports of sleep disturbance ranging from 3% to 77.1% and nightmares ranging from 20.3% to 80.8%.

The clinical relevance of our findings suggests prazosin use at doses 1 to 4 mg at bedtime for treatment of nightmares associated with PTSD seems effective. There was overall marked reduction in frequency and intensity of nightmares in all 6 case reports. There was also significant improvement in associated hyperarousal and intrusive symptoms with use of prazosin.

TABLE 1. Summary of Results

Reference	Age, y/Sex	Source of Trauma	Dose mg/d	Outcome	Adverse Effects	Additional Comments
Brkanac et al,[9] 2003	15/Female	Physical and sexual assault, parental neglect	4	Improved sleep with no nightmares and global clinical improvement	No	Reduction in depressive and associated behavioral symptoms
Fraleigh et al,[7] 2009	16/Male	Witnessed friend's violent death	1.5	Frequency of nightmare dropped from 7/7 to 0/7 nights per week	No	Comorbid conduct disorder; nightmares increased in both frequency and intensity flowing discontinuation
Strawn et al,[6] 2009	16/Female	Robbery victim	2	Absence of nightmares with return of normal sleep latency	No	Attenuation of hyperarousal symptoms was noted as well
Strawn and Keeshin,[10] 2011	7/Male	Sexual assault	1	Absence of nightmares, normal sleep latency and reduced hyperarousal symptoms	? Weight gain	Comorbid ADHD
Oluwabusi et al,[8] 2012	(1) 16/Female, (2) 15/female	(1) Physical and sexual assault, (2) sexual abuse	(1) 3, (2) 3	(1) Nightmare subsided and sleep pattern readjusted to normal, (2) sleep-related symptoms of PTSD significantly subsided	(1) No, (2) transient dizziness lasting 1 wk	Both had improvement in some symptoms of PTSD with cognitive behavioral therapy with nightmares persisting prior to initiation of prazosin
Racin et al,[4] 2014	10/Male	Childhood abuse and neglect	2	Relief from nightmare and improved quality of sleep	No	Increase in aggressive behavior and nightmares following discontinuation

Furthermore, prazosin use was well tolerated in all 6 case reports with no reported adverse effect except for weight gain and increased body mass index in a 7-year-old boy after 11 months of therapy. Given the high reported prevalence of PTSD-related nightmares in children and adolescent and its significant burden, our findings will help alleviate this burden by improving overall symptoms of PTSD.

The data available from this systematic review indicate that prazosin has been successfully used in the treatment of PTSD-related nightmares in children and adolescents. Despite a search strategy that was optimized toward identifying studies using prazosin for PTSD-related nightmares in children and adolescents, we were able to find only case reports, and all our data gathered from them suggest there is scant evidence to guide physicians in the psychopharmacologic treatment of PTSD-related nightmares in children and adolescents.

There has been documented case report evidence for the efficacy of prazosin use in treatment of PTSD-related nightmares in children and adolescents with no clinical trials. The results from our review are promising; however, large well-controlled RCTs need to be done so as to determine the safety and efficacy of prazosin use in the treatment of PTSD-related nightmares.

The strengths of this study include the systematic nature of collection of data using different search terms from 5 large databases and that there was no language restriction. The limitations of this review include the age restriction in our search criteria and lack of larger studies for the pediatric age group, with all our data coming from case reports alone. Of note, there are RCTs published in the adult population, but none in children.

CONCLUSIONS

Nightmares associated with PTSD have considerable comorbidity. Currently, there are no Food and Drug Administration–approved medications for treatment of nightmares associated with PTSD in children. Our review highlights that prazosin helps with pediatric PTSD-related nightmares. This positive outcome gives room for consideration of this medication in the treatment of children and adolescents with PTSD-related nightmares. Given that there are no RCTs in children, we recommend that RCTs be conducted to assess efficacy and safety of prazosin.

Traumatized children often suffer from other comorbid psychiatric illnesses such as depression and anxiety, which can be sequelae of PTSD. These comorbidities can be reduced if PTSD symptoms are addressed adequately. The ultimate goal for a clinician is to reduce morbidity and mortality and improve quality of life in children and adolescents with PTSD, which prazosin can help with.

AUTHOR DISCLOSURE INFORMATION

The authors declare no conflicts of interest.

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