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The Off-Label Use of Prazosin for Sleep Disturbances in Noncombat Posttraumatic Stress Disorder

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Abstract
Background: Posttraumatic stress disorder (PTSD) is a form of anxiety disorder that arises after exposure to a traumatic event or stressor. It is characterized by persistent invasive thoughts, emotional detachment, hypervigilance and sleep disturbances. These sleep disturbances include nightmares, insomnia and distressed awakenings and are often refractory to multiple medications, including SSRIs, which are the only FDA approved medication for PTSD. Prazosin is an alpha-1 adrenergic antagonist that has been studied for use in nighttime symptoms of PTSD in civilian populations, however most data exists for its use in combat-related PTSD. This review examines the differences in these two populations and investigates the off-label use of prazosin for sleep disturbances in noncombat posttraumatic stress disorder.

Methods: Exhaustive search of available medical literature via MEDLINE, CINAHL, PILOTS, and PsychINFO databases using combinations of the terms PTSD, Stress Disorder, Prazosin, Alpha Antagonist and Alpha Blocker. Inclusion criteria were set to incorporate studies that used prazosin to treat nighttime symptoms of PTSD in a noncombat, non-military population. Exclusion criteria eliminated studies pertaining to combat PTSD, military or veteran population. Non peer-reviewed Letters to Editor were also excluded.

Results: Four studies, including one randomized control trial, one retrospective cohort, one case series and one case study were found.

Conclusion: Prazosin has potential as a treatment for the sleep disturbances of noncombat related PTSD. Both the prevalent female gender and heterogeneity of individual traumas in this civilian population were much different than previous trials and reviews that examined combat PTSD. While the demographics and experiences were diverse compared to the veteran population, the positive response to prazosin was similar to past findings. While larger, randomized and placebo-controlled trials are needed for FDA approval, the current off-label use of prazosin is demonstrated in the existing literature as efficacious.

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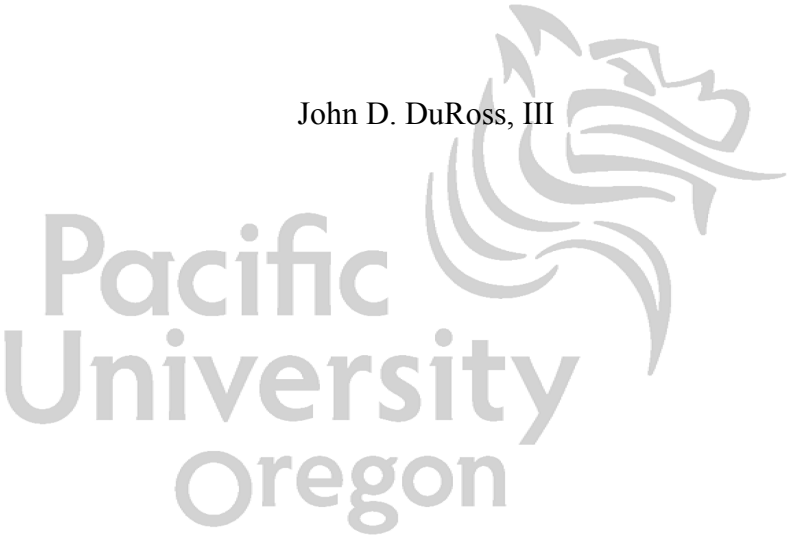
John D. DuRoss, III



A Clinical Graduate Project Submitted to the Faculty of the

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Clinical Graduate Project Coordinators: Annjanette Sommers MS, PA-C & Rob Rosenow PharmD, OD

Biography

Biography: John “Chip” DuRoss was born and raised in Ohio but quickly fled west for a life in the mountains. After graduating from the University of Montana in Missoula, Chip took a formative trip to South America, where he continued his lifelong pursuit of the Spanish language and more importantly, regained the love of his high school sweetheart who would later become his wife. After 7 years as a Snowbird ski patroller and 3 summers as a wildland firefighter, Chip decided the seasonal lifestyle was more attractive in theory than in practice. Putting his EMT training to use as an emergency room technician at the University of Utah, he began the process of applying for PA school. Embracing the “Road Less Travelled”, he and his wife decided to leave behind the practical option for the adventurous move to Oregon for graduate school.

Abstract

Background: Posttraumatic stress disorder (PTSD) is a form of anxiety disorder that arises after exposure to a traumatic event or stressor. It is characterized by persistent invasive thoughts, emotional detachment, hypervigilance and sleep disturbances. These sleep disturbances include nightmares, insomnia and distressed awakenings and are often refractory to multiple medications, including SSRIs, which are the only FDA approved medication for PTSD. Prazosin is an alpha-1 adrenergic antagonist that has been studied for use in nighttime symptoms of PTSD in civilian populations, however most data exists for its use in combat-related PTSD. This review examines the differences in these two populations and investigates the off-label use of prazosin for sleep disturbances in noncombat posttraumatic stress disorder.
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Keywords: prazosin, stress disorder, PTSD, nightmares, alpha antagonist, alpha blocker

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Appendix A……..….....PTSD Checklist-Civilian Version

List of Abbreviations

CAPS……Clinician Administered PTSD Scale

CAPS-SX……...CAPS Symptom Version

CGI-C……..Clinical Global Impressions-Change

CGI-I……..Clinical Global Impressions-Improvement

CIC-N……Clinical Impression of Change-Nightmares

DSM-IV……..Diagnostic and Statistical Manual of Mental Disorders, 4th Edition

FDA……..Food and Drug Administration

NNDA……Non Nightmare Distressed Awakenings

PCL-C……..PTSD Checklist-Civilian Version

PTSD……..Posttraumatic Stress Disorder

REM……..…..Rapid Eye Movement

SSRIs…….....Selective Serotonin Reuptake Inhibitors

The Off-Label Use of Prazosin for Sleep Disturbances in Noncombat Posttraumatic Stress Disorder

BACKGROUND

Posttraumatic stress disorder (PTSD) is an anxiety disorder that arises after exposure to a traumatic event or stressor. It is characterized by persistent invasive thoughts, emotional detachment, hypervigilance and sleep disturbances.[1] PTSD was first recognized in the military population and throughout history has often been described as related to combat.[2] However, with the frequent exposure to trauma to which civilians from the general population are exposed, the prevalence of PTSD outside the combat population has greatly increased. Approximately 5.2 million adults suffer from PTSD throughout a given year, and the estimated lifetime prevalence of PTSD is 7.8%.[3,4]

Sleep Disturbances

70-87% of those with PTSD develop sleep disturbances, including nightmares, insomnia, and distressed awakenings.[5,6] Of the wide array of PTSD symptoms, these are some of the hardest to treat and are often refractory to multiple medications and treatment modalities. Furthermore, the Food and Drug Administration (FDA) currently only approves the use of the selective serotonin reuptake inhibitors (SSRIs) sertraline and paroxetine for use in PTSD.[7] Unfortunately, both of these medications have shown little improvement in sleep related symptoms and, in some cases can worsen sleep and increase arousals due to their known stimulating effects on sleep.[7]

Rating Scales and Assessments

Several methods have been developed for assessing posttraumatic stress disorder and the array of commonly experienced symptoms. Those found in the following studies will be discussed here. The Diagnostic and Statistics Manual, 4th Edition, Text Revision (DSM-IV-TR) specific criteria for the diagnosis of PTSD, including exposure to a traumatic event (Criterion A), persistent re-experiencing (Criterion B), avoidance of stimuli and numbing of responsiveness (Criterion C), hyper-arousal (Criterion D), symptoms lasting for at least one month (Criterion E) and a significant impairment of functioning (Criterion F).[8] The PTSD Checklist-Civilian Version (PCL-C) is an evaluation of symptoms that relies on self report, and when used in combination with the DSM-IV criteria, can be a sensitive and specific diagnostic tool.[9] The Clinician Administered PTSD Scale (CAPS) is a widely accepted method for assessing posttraumatic stress disorder as it incorporates a 30 item review of all PTSD symptoms. Item #2 ("recurrent distressing dreams") and item #13 ("difficulty falling asleep/ staying asleep") are common measurements of sleep-related symptoms of PTSD. CAPS has also been modified to include a Non-Nightmare Distressed Awakenings (NNDA) scale.[10] Also more specific is the CAPS One Week Symptom Version (CAPS-SX) that combines a nightmare rating with an insomnia rating to measure intensity and frequency of these symptoms. To differentiate between pathologic and normal dream content, the PTSD Dream Rating Scale (PDRS) was developed for the civilian population. Improvement in nightmares after treatment is measured with the Clinical Impression of Change-Nightmares (CIC-N) scale. On a broader spectrum, changes and improvement of overall PTSD are often measured via the Clinical Global Impression-Change (CGI-C) score and Clinical Global Impression-Improvement (CGI-I) scores, respectively. One study uses several

variations of objective measures of Rapid Eye Movement (REM), with use of a portable device, called REMView, that patients use at home.[10]

Prazosin

Prazosin is a peripherally and centrally acting alpha antagonist that has been most often studied for the use of sleep-related symptoms of PTSD in the combat and veteran populations.[11-14] While traditionally used for the treatment of hypertension and benign prostatic hypertrophy, prazosin is believed to be effective due to the blocking activity of central alpha adrenergic receptors, which are often excessively active in PTSD patients.[7] Fewer studies have involved populations outside the military, leading to less information regarding the use of prazosin for noncombat PTSD sleep symptoms. The differences in these two populations abound.

The populations differ in gender. Military populations are predominantly male, and thus, studies from this population inherently trend toward males.[15] In fact, six out of the seven studies that were included in a recent systematic review of prazosin use for PTSD were performed in a combat or military veteran population, therefore 98% of the patients included in the review were male (see Figure 2).[7] In contrast, in the general population, there is approximately a 2 to 1 female to male ratio for PTSD.[16] Women are more likely than their male counterparts to have a post-traumatic stress response and the overall prevalence of PTSD is higher.[17,18] There are important differences between males and females in PTSD. After a trauma, women are more likely to develop PTSD. Furthermore, depression as a co-morbidity, longer recovery times, and higher prevalence of long-lasting PTSD are all characteristic of PTSD in females when compared to males.[17] When we look outside the military and examine a more female dominated sample, we see PTSD with a different perspective.

Secondly, the details of the trauma experiences differ in these populations. In noncombat related PTSD, a much wider variation of trauma exists when compared to combat PTSD (see Figure 2). From sexual abuse to car accidents and from kidnapping to severe medical illnesses, traumas outside combat zones tend to deal with a large spectrum of incidents.[4] While certainly a combat setting can be heterogeneous, including firefights, helicopter accidents, or witnessing civilian death, most PTSD from a military perspective may arise from direct combat. In fact, Hoge et al[19] found that there was a direct linear increase in prevalence of PTSD when compared to the number of firefights that a soldier was involved in. Furthermore, both being injured in combat and killing enemies also increases the likelihood of developing PTSD.[19,20,21,16] This supports the idea that posttraumatic stress disorder in a military population develops from specific combat experiences. The homogeneity of precipitating event is in stark contrast to the vast array of possibilities in the civilian population, and this may be an important factor.

Because of the differences between combat veteran patients and the general population, including gender and heterogeneity of traumatic experience, any treatment regime should be evaluated with the perspective, that those outside the military are a distinct population. For this reason, the following systematic review of the literature asks, whether, in patients with noncombat related PTSD, off-label use of prazosin improves trauma related nightmares and sleep disturbances.

METHODS

An exhaustive search was performed using MEDLINE, CINAHL, PILOTS, and PsychINFO databases. The articles were found in the four databases, using combinations of the terms PTSD, Stress Disorder, Prazosin, Alpha Antagonist and Alpha Blocker.

Inclusion criteria were set to incorporate English language studies that used prazosin to treat nighttime symptoms of PTSD in a noncombat, non-military population. Exclusion criteria eliminated studies pertaining to combat PTSD, military or veteran population. Non peer-reviewed 'Letters to Editor' were also excluded.

RESULTS

The comprehensive literature search in the four major databases, in conjunction with the specific inclusion and exclusion criteria revealed four studies. These include one randomized control trial, one retrospective cohort study, one open-label case series and one case study (see Table 1).

Randomized Control Trial

During 2004 and 2005, Taylor et al[10] conducted a crossover style study in which 13 randomized outpatients with chronic civilian PTSD participated in both the treatment arm and the placebo arm of the study. Participants met DSM-IV criteria for PTSD, scored at least 40 on the PTSD Checklist-Civilian Version, and had a minimum score of 4 on both the CAPS items #2 and #13. After excluding 2 subjects who had reported orthostatic dizziness with a test dose, the trial subjected the remaining blinded patients to two 3 week periods of both treatment and placebo with a 1 week washout period between stages. Medication (or placebo) was initiated at 1 mg and titrated upward by 1 mg increments over the course of 10 days based on therapeutic or adverse effects. The final dose was then maintained for 11 days.[10]

Outcomes to be measured in this trial were objective sleep measures including sleep time, Rapid Eye Movement (REM) latency, REM duration, and sleep onset latency as well as

subjective nightmare and overall PTSD symptoms. Adverse events were also monitored and discussed for both the treatment and placebo arms of the trial.[10]

With a mean prazosin dose achieved of 3.1 +/- 1.3 mg, (vs. mean placebo dose of 3.2 +/- 1.2 mg), this study showed significant improvement in multiple sleep-related PTSD symptoms in the population treated with prazosin. The prazosin group had a longer total sleep time (374 +/- 86 min vs. 280 +/- 105 min, $p < .01$), as well as a longer REM sleep time (138 +/- 63 min vs. 97 +/- 70 min, $p < .01$). When compared to the placebo group, those treated with prazosin also had decreased sleep REM latency, a measure of the time period between falling asleep and starting REM (95 +/- 62 min vs. 30 +/- 20 min, $p < .05$). In addition to longer REM time, and a faster initiation of REM sleep, each REM period had a longer duration on average for the prazosin treatment arm of this trial (27 +/- 9 min vs. 18 +/- 9 min, $p < .05$). There was no significant difference in sleep onset latency between the two groups.[10]

In addition to the objective sleep measures, several clinical outcomes were improved in the prazosin group, including the CAPS "recurrent distressing dreams" (item #2), Non-nightmare Distressed Awakenings (NNDAs), CGI-I scores, the PTSD Dream Rating Scale and PTSD Checklist-Civilian Version (PCL-C). The CAPS "difficulty falling asleep/staying asleep (item #13) showed an improvement but was not statistically significant. Adverse effects did not differ between the placebo group and the treatment group, as dizziness occurred 3 times in each group.[10]

Conclusions from this trial were that prazosin, in addition to improving clinical PTSD sleep related symptoms, provided objective improvements to total sleep time, REM sleep and REM duration. The authors also felt that prazosin was well tolerated.[10]

Retrospective Cohort

Boyton et al[22] conducted a retrospective chart review which analyzed the data from 23 refugees. All patients from The International Medicine Clinic in Seattle, Washington that had been diagnosed with chronic PTSD and had been treated with prazosin between October 2004 and November 2005 were included in the review. The cohort, which was made up of 15 females and 8 males, included patients from Afghanistan, Albania, Cambodia, Ethiopia, Gambia, Iraq, Somalia, and Vietnam. These patients were exposed to a variety of traumas, including kidnapping, sexual abuse and witnessing war atrocities such as death and torture.[22]

Changes in nightmare severity were measured through the CAPS "recurrent distressing dreams" item before initiation and after 8 weeks of a stable dose of prazosin. The CGI-C was used to measure the overall severity of PTSD, after a stable dose of prazosin had likewise been given for 8 weeks.[22]

The International Medicine Clinic's standard is to treat patients with an initial dose of prazosin of 1 mg, then slowly titrate up until either, symptoms improve, or adverse effects become unmanageable. Results show a statistically significant reduction in CAPS score after 8 weeks of treatment with a stable dose of prazosin in this population. The baseline mean was 6.91 (SD = 0.85) before treatment. After, the mean CAPS score was 2.61 (SD = 1.67). These results indicate that, at baseline, the participants had experienced nightmares daily or almost daily, with severe or incapacitating distress, and with difficulty returning to sleep. The scores after 8 weeks of treatment indicated that the subjects experienced nightmares an average of 1-2 times per week with mild or moderate distress and had regained the ability to fall back asleep. Statistically, the improvement in the CAPS score was found to be significantly related to both dose and duration of medication received. Overall PTSD severity, as measured by the CGI-C,

also showed improvement. After treatment, 73.8% of the subjects reported either marked or moderate improvement in overall symptoms. Though not objectively measured, the authors report that prazosin was well tolerated, with dizziness being the most common reported adverse effect. One of the six reported patients to discontinue the medicine after several months did so because of dizziness, while the others did so due to significant improvement.[22]

Open-Label Case Series

In this open label trial conducted by Taylor et al,[23] five outpatients were treated with prazosin for their sleep related symptoms of PTSD. They were to be assessed before treatment initiation, after two weeks of treatment, and again after 6 weeks of treatment. Measured outcomes included CAPS-SX Nightmare score and CAPS-SX Insomnia score at these time intervals as well as both a CGI-C and a CIC-N score at the completion of 6 weeks of treatment.[23]

Patients of this outpatient clinic were identified with the specific requirement that they meet DSM-IV criteria for diagnosis of PTSD, a score of at least 80 on the CAPS and a score of at least 4 out of 8 on the CAPS-SX. They also had to have PTSD symptoms as their primary reason for seeking treatment and have no history of alcohol or substance abuse within the last 6 months. With these criteria, five consecutive patients were identified. The group included a 53 year old unemployed woman with a history of abuse and neglect, a 35 year old male carpenter who had been severely burned at work, a 53 year old woman exposed to ritual violence and forced into prostitution as part of a satanic cult, a 58 year old woman with a history of a life threatening pulmonary embolus and a 40 year old nurse who was the victim of abusive parents and had to escape her burning house as a child. All patients were started on prazosin at a dose on 1 mg at bedtime. After 2 weeks, if there was no improvement of symptoms, the dose was

increased to 2 mg. If necessary, a morning dose was added for daytime symptoms. Vital signs were recorded only if patients reported dizziness.[23]

All five patients treated with prazosin had improvement in all measured categories. The frequency and severity of both nightmares and insomnia were reduced after two and six weeks of treatment. Furthermore, the CGI-C and CIC-N scores were improved in all five patients. It should be noted that while it was not objectively measured, varying degrees of follow up with these patients is discussed in this article. Four out of five patients are reported to have continued prazosin for several months with sustained benefits. The fifth patient, who had major improvement during the trial and no side effects decided to discontinue the prazosin, and has had continued improvement without the medication. Authors felt that this patient may have been a placebo responder. One participant noted dizziness as an adverse effect. Otherwise, the authors report prazosin as being well tolerated.[23]

In a varied outpatient civilian population with diverse individual traumatic experiences, such as this one, the conclusions of this small case series were that prazosin was successful in improving sleep related symptoms of PTSD. A quick patient response to treatment was felt to indicate that the prazosin may be acting directly on the alpha-1 adrenergic receptors. The authors recognize however, that several limitations exist, including a small sample size and no placebo control, making it difficult to say that the changes experienced are statistically significant. They also discussed the possibility that the concomitant use of psychotropic medications in 4 of the 5 subjects, could have enhanced the effect of prazosin. Regardless, this small case series was thought to offer justification to develop a larger, blinded placebo-controlled trial of prazosin for sleep-related PTSD symptoms.[23]

Case Study

In the case study by Coupland[24], civilian firefighter with PTSD related insomnia nightmares was successfully treated with prazosin. The patient met criteria for PTSD but not for depression and described severe symptoms including repeated awakenings and frequent nightmares. This patient had been subjected to a prior sleep study which ruled out sleep apnea but did show awakenings from light sleep as well as decreased total sleep and REM sleep. The patient had tried several other treatment modalities, including psychotherapy, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and tricyclic antidepressants along with combinations of benzodiazepines, and other sedatives.[24]

Prazosin 1 mg was initiated at bedtime for one week and then titrated up 1 mg every three to four days. The patient reported initial light-headedness and tiredness upon rising, both of which resolved. He also reported dry mouth in the morning that resolved with breakfast. The patient reported improving symptoms at week three, and had a stable dose of 6 mg by week four, at which time he reported greatly improved sleep and decrease in nightmares.[24]

DISCUSSION

In all four of the studies found with the exhaustive literature search and reviewed above, prazosin appears to be both safe and efficacious for the treatment of sleep-related symptoms of noncombat PTSD.[10, 22-24]

Furthermore, the results of this review demonstrate both the heterogenous nature and female prevalence of noncombat PTSD. In previous studies and reviews of this topic, the majority of subjects were from a military and male population.[1,7,25] In this review 71.4% of the subjects in the four studies were female, and the details of the individual trauma varied greatly,

ranging from decades-old child abuse to severe medical illnesses. This diverse nature and gender distribution highlights the need to analyze this population separately. Each of the four studies was a unique addition to the cumulative result.

The randomized control trial[10] provided an important indicator that, when compared to placebo, prazosin shows a significant improvement in sleep-related symptoms of PTSD in this population.[10] Furthermore, this study is unique in that it measured objective sleep outcomes, using the in-home technology of REMView.

The retrospective study of refugees with PTSD[22], while not a trial of traditional civilians, met criteria for this systematic review, as the subjects did not have combat-related PTSD and were not part of a military or veteran population.[22] Furthermore, the heterogeneity of their trauma experiences and demographic profile augment the perspective that this systematic review sought to achieve, which is a separation from the traditional military population with combat-PTSD.

The clear inadequacies of case series and case studies certainly apply to those included in this review. The lack of placebo control, blinding and randomization limit their statistical significance.[23, 24] However, they provide documented examples of prazosin use for sleep related symptoms of PTSD in the civilian population. Both studies demonstrate a response to the off-label use of this medication and how it may be a safe alternative to the currently approved PTSD medications when patients present with irretractable sleep symptoms such as insomnia and nightmares.

Certainly a limitation of the research is the fact that there exists a limited supply of quality studies of prazosin for sleep disturbances in the noncombat PTSD population. Furthermore, the only placebo-controlled trial in this review contains a small sample size, as do

the retrospective cohort and case series. It could be debated whether or not the inclusion of the refugee population is a limitation to this review. A cohort of refugees may represent a very different population from the general citizenry of the United States. Their trauma experiences may include otherwise unthinkable atrocities such as genocide and civilian death in their war-torn country of origin. However, an argument could be made that by including such a diverse and international population, it is possible to further expand the recommendation for the use of prazosin in varied populations. As the exclusion criteria were set up specifically to eliminate combat-related PTSD, this study does fit into our review.

More limits of the existing research are evident. The three studies that were not controlled by placebo did not have the burden of establishing that prazosin was superior to placebo effect.[22-24] The retrospective cohort[22], case series[23] and case study[24] were all non-blinded and open label, so bias may have been present in both the patients and evaluators. The exclusion of subjects with orthostatic dizziness with a test dose by Taylor et al[10] may distort the representation of prazosin as being well tolerated in the placebo-controlled study. Also of note, Dr. Nick J. Coupland, author of the published case study, declares past research funding by Pfizer, the manufacturer of Minipress, the branded form of prazosin.[24]

Clearly, there is a need for further randomized, double blind, placebo controlled studies of prazosin use for noncombat related PTSD. Sample sizes should be larger and objective sleep measures, such as REMView used in the study by Taylor et al, should be continued to be used when possible.

CONCLUSION

In summary, prazosin shows considerable potential as an agent for the improvement of sleep-related symptoms of noncombat related PTSD. The gender differences and heterogeneity of trauma details found in the various studies of this review are in sharp contrast to the male-dominated, combat-specific PTSD of previous studies and previous systematic reviews. These differences provided the impetus for reviewing the literature pertaining to the noncombat population. After separating the populations and conducting this review, it does appear that the studies' results are consistent with the findings in military populations with combat PTSD.

It can be said with confidence that prazosin should be considered for sleep related symptoms of noncombat PTSD. This alpha-1 adrenergic receptor antagonist, due to its centrally-acting properties likely has an impact on the alpha-1 receptors that are often overly stimulated in PTSD patients. Further randomized, placebo-controlled studies with larger sample sizes from this population are recommended. A study by Murray Raskind is in process currently and it is expected to be completed in November 2010.[26] This is planned to be a larger, randomized control study in collaboration with the National Institute of Mental Health and will look at the response to prazosin versus placebo in patients receiving an SSRI and psychotherapy. As the FDA currently only approves the SSRIs sertraline and paroxetine for use in PTSD, more of these comparison and combination studies should take place to demonstrate efficacy over the standard practice and potential as an approved additive medication.

The above findings have important implications to both mental health clinicians and primary care providers. Even as the United States is currently engaged in war and much attention is paid to combat populations, PTSD in civilians is quite prevalent, affecting 7-8% of the U.S. population at some time during their lives.[3, 27] The general population is subjected to

noncombat trauma daily here in the U.S., including terrorist attacks, motor vehicle accidents, natural disasters, assaults, robberies, kidnappings and severe illnesses, this is a population that needs to be recognized as susceptible to posttraumatic stress disorder. Fortunately, when their symptoms include sleep-related disturbances, which the majority of PTSD patients experience, a clinician can be confident in the safe, efficacious use of prazosin.

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TABLE 1. Summary Matrix of Reviewed Articles

Study	Patients/ Population	Intervention	Comparison	Outcome(s)	Jadad Score	Results
Taylor FB et al[10], 2008. Randomized Placebo-controlled Crossover Trial	Outpatients with chronic civilian trauma PTSD, frequent nightmares and sleep disturbances. n= 13.	Prazosin, initiated at 1mg at bedtime, then titrated up by 1 mg increments every 2-3 days until therapeutic effect. Stable dose then maintained for 11 days.	Placebo, also titrated up over same time frame and intervals as intervention group.	CAPS item #2, CAPS item #13, NNDA's, CGI-I scores, PTSD Dream Rating scale, PCL-C	4	Multiple objective and clinical improvements
Boynton L et al[22], 2009. Retrospective cohort study	Outpatients at primary care clinic. All patients had met DSM-IV criteria for PTSD, and had been treated with prazosin. n = 23.	Prazosin, 1 mg at bedtime, with the dose titrated up until either symptoms significantly improved or adverse drug reactions developed.	No comparison	CAPS item #2, CGI-C scores	0	Improvement in average CAPS score and 73.8% with moderate or marked Improvement in overall PTSD
Taylor F et al[23], 2002. Case Series	Consecutively identified outpatients with PTSD and sleep disturbances. n = 5.	Prazosin, initiated at 1 mg at bedtime. As needed, dose increased to 2 mg at bedtime. A morning dose was added for daytime symptoms if needed.	No comparison	CGI-C scores, CIC-N scores, CAPS-SX severity scores with insomnia and nightmare severity sub-scores	0	All 5 patients showed improvement in measured outcomes
Coupland N[24], 2009. Case Study	Civilian firefighter with PTSD, insomnia, and distressing nightmares. n = 1	Prazosin, 1 mg at bedtime for 1 week, then increasing in 1 mg increments every 3-4 days to 6 mg as stable dose.	No comparison	Subjective descriptions of restlessness, sleep, and nightmares	0	Patient reported improved sleep and decreased night symptoms

FIGURE 1. Gender Distribution

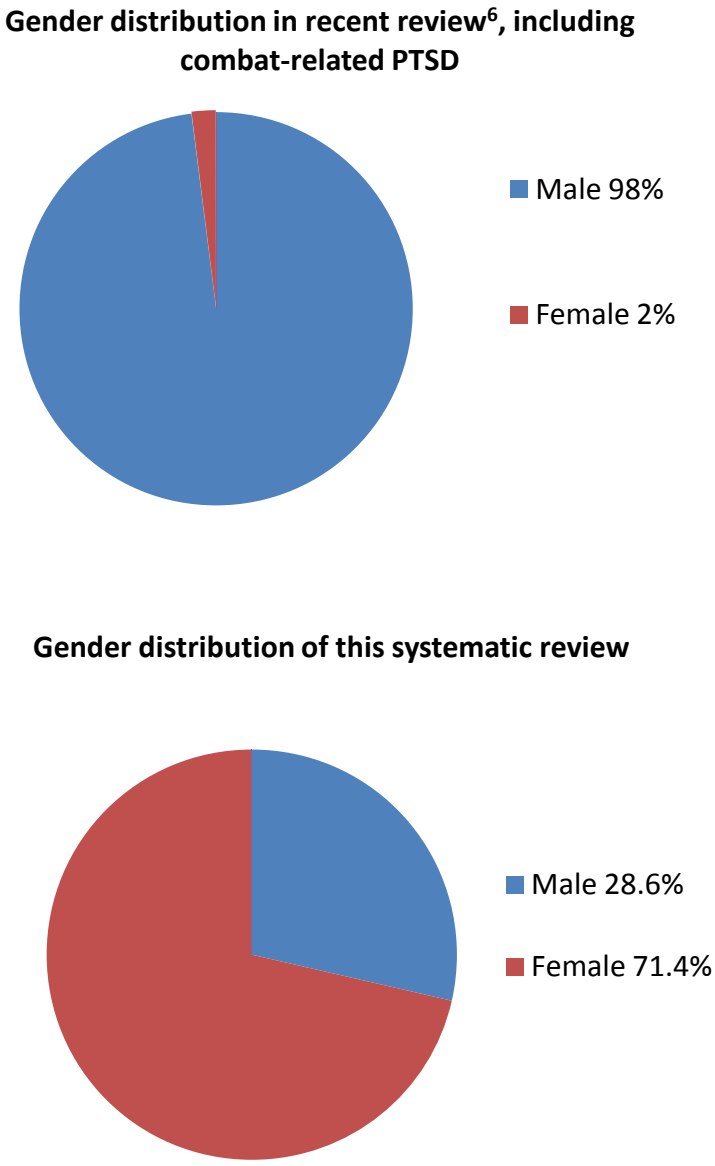
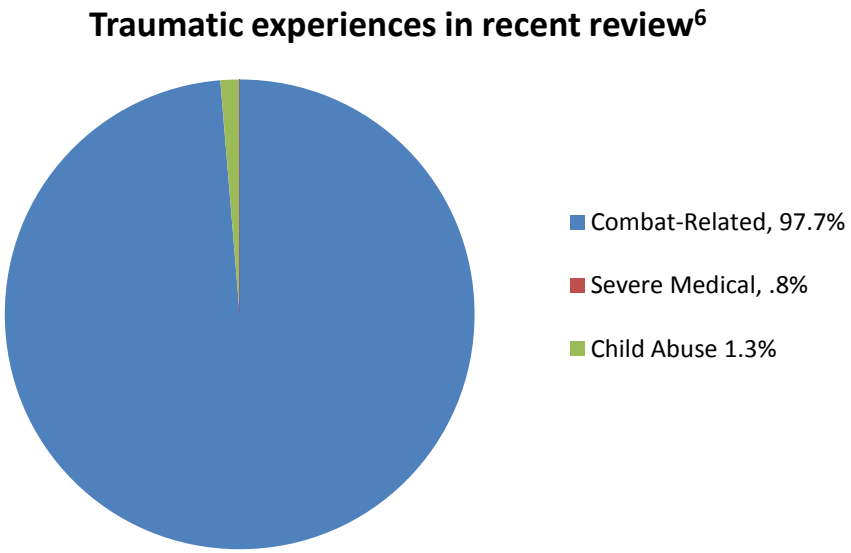
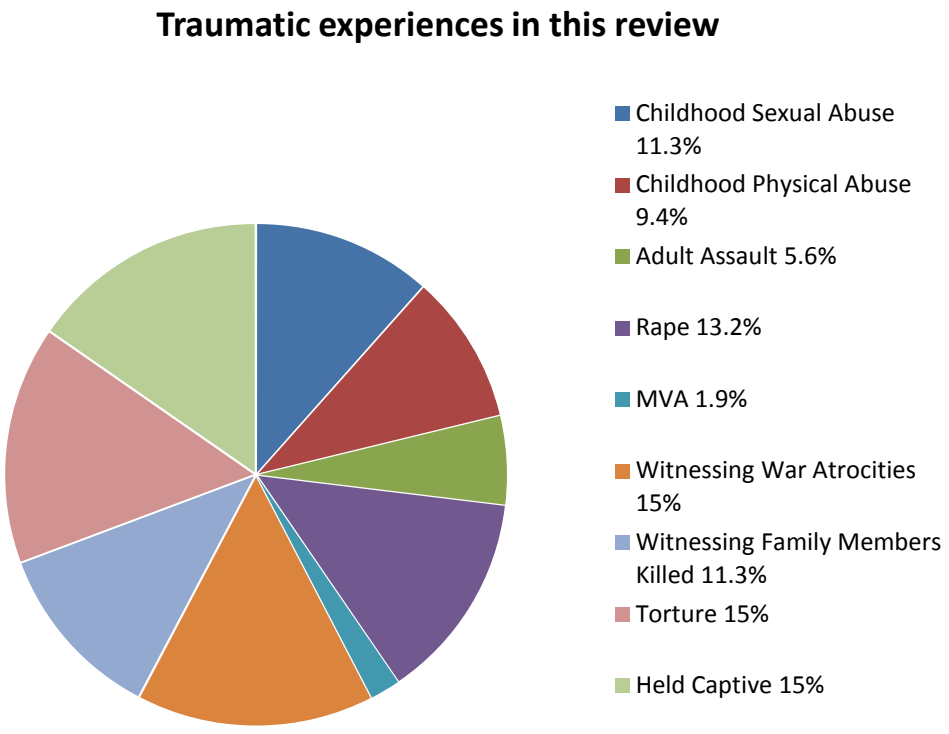


FIGURE 2. Heterogeneity of Traumatic Experiences





APPENDIX A

PTSD Checklist – Civilian Version (PCL-C)

Patient's Name: _____

No.	Response:	Not at all (1)	A little bit (2)	Moderately (3)	Quite a bit (4)	Extremely (5)
1.	Repeated, disturbing *memories, thoughts,* or *images* of a stressful experience from the past?					
2.	Repeated, disturbing *dreams* of a stressful experience from the past?					
3.	Suddenly *acting* or *feeling* as if a stressful experience *were happening again* (as if you were reliving it)?					
4.	Feeling *very upset* when *something reminded* you of a stressful experience from the past?					
5.	Having *physical reactions* (e.g., heart pounding, trouble breathing, or sweating) when *something reminded* you of a stressful experience from the past?					
6.	Avoid *thinking about* or *talking about* a stressful experience from the past or avoid *having feelings* related to it?					
7.	Avoid *activities* or *situations* because *they remind you* of a stressful experience from the past?					
8.	Trouble *remembering important parts* of a stressful experience from the past?					
9.	Loss of *interest in things that you used to enjoy?*					
10.	Feeling *distant* or *cut off* from other people?					
11.	Feeling *emotionally numb* or being unable					

	to have loving feelings for those close to you?					
12.	Feeling as if your *future* will somehow be *cut short*?					
13.	Trouble *falling* or *staying asleep*?					
14.	Feeling *irritable* or having *angry outbursts*?					
15.	Having *difficulty concentrating*?					
16.	Being *"super alert"* or watchful on guard?					
17.	Feeling *jumpy* or easily startled?					

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