

Prazosin and doxazosin for PTSD are underutilized and underdosed

Often, clinicians tend to focus on the diagnosis and treatment of psychiatric disorders, such as psychosis, bipolar disorder, depression, anxiety, insomnia, and substance use disorders (SUD), but posttraumatic stress disorder (PTSD) often is overlooked and underdiagnosed,¹ especially when comorbid with another psychiatric disorder such as SUD.

The primary symptoms of PTSD are recurrent and include intrusive memories and dreams of the traumatic events, flashbacks, hypervigilance, irritability, sleep disturbances, and persistent avoidance of stimuli associated with the traumatic event. According to the National Comorbidity Survey, the estimated lifetime prevalence of PTSD among adults is 6.8% and is more common in women (9.7%) than men (3.6%).² Among veterans, the prevalence of PTSD has been reported as:

- 31% among male Vietnam veterans (lifetime)

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Disclosure

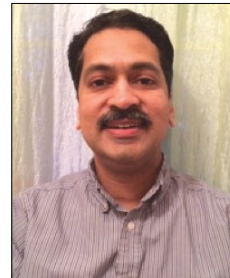
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- 10% among Gulf War veterans
- 14% among Iraq and Afghanistan veterans.³

Why is PTSD overlooked in substance use?

Among individuals with SUD, 10% to 63% have comorbid PTSD.⁴ A recent report underscores the complexity and challenges of SUD–PTSD comorbidity.⁵ Most PTSD patients with comorbid SUD receive treatment only for SUD and the PTSD symptoms often are unaddressed.⁵ Those suffering from PTSD often abuse alcohol because they might consider it to be a coping strategy. Alcohol reduces hyperactivation of the dorsal anterior cingulate cortex caused by re-experiencing PTSD symptoms. Other substances of abuse, such as *Cannabis*, could suppress PTSD symptoms through alternate mechanisms (eg, endocannabinoid receptors). All of these could mask PTSD symptoms, which can delay diagnosis and treatment.

SUD is the tip of the “SUD–PTSD iceberg.” Some clinicians tend to focus on detoxification while completely ignoring the underlying psychopathology of SUD, which may be PTSD. Even during detoxification, PTSD should be aggressively treated.⁶ Lastly, practice guidelines for managing SUD–PTSD comorbidity are lacking.



Maju Mathew Koola, MD

Prazosin and doxazosin, which have been used for PTSD, also can treat substance abuse; this ‘two birds with one stone’ approach could become more common in clinical practice

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Targeting mechanisms of action

Noradrenergic mechanisms have been strongly implicated in the pathophysiology of PTSD. However, selective serotonin reuptake inhibitors, such as sertraline and paroxetine, are the only FDA-approved pharmacotherapy options for PTSD, although their efficacy is limited, perhaps because they are serotonergic.

Prazosin, an alpha-1 (α -1) adrenergic antagonist that is FDA-approved for hypertension and benign prostatic hypertrophy, has been studied for treating nightmares in PTSD.⁷ Prazosin has shown efficacy for nightmares in PTSD and other daytime symptoms, such as flashbacks, hypervigilance, and irritability.⁸ Several studies support the efficacy of prazosin in persons suffering from PTSD.⁹⁻¹¹ Use of lower dosages in clinical trials might explain why prazosin did not separate from placebo in some studies. (See this article at CurrentPsychiatry.com for a *Table* summarizing studies of prazosin dosing for PTSD.)

In a study of 12,844 veterans, the mean maximum prazosin dosage reached in the first year of treatment was 3.6 mg/d, and only 14% of patients reached the minimum Veterans Affairs recommended dosage of 6 mg/d.¹⁷ The most recent (March 2009) American Psychiatric Association practice guidelines recommend prazosin, 3 to 15 mg at bedtime.¹⁸

Prazosin has a short half-life of 2 to 3 hours and duration of action of 6 to 10 hours. Therefore, its use is limited to 2 or 3 times daily dosing. Higher (30 to 50 mg) and more frequent (2 to 3 times per day) dosages^{8,12,13} might be needed because of the drug's short half-life.

Doxazosin. Another α -1 adrenergic drug, doxazosin, 8 to 16 mg/d, has shown benefit for PTSD as well.^{14,15} Doxazosin, which has a longer half-life

(16 to 30 hours), requires only once-daily dosing.¹⁶ The most common side effects of prazosin and doxazosin are dizziness, headache, and drowsiness; syncope has been reported but is rare.

Prazosin and doxazosin also are used to treat substance abuse, such as alcohol use disorder¹⁹⁻²¹ and cocaine use disorder.^{22,23} This "two birds with one stone" approach could become more common in clinical practice.

Until a major breakthrough in PTSD treatment emerges, prazosin and doxazosin, although off-label, are reasonable treatment approaches.

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Table

Prazosin dosing for posttraumatic stress disorder

Studies	Men	Women
Raskind et al, (clinicaltrials.gov NCT00532493) ^a	5 mg in the morning, and 15 mg at bedtime	2 mg in the morning, and 10 mg at bedtime
Raskind et al, ¹ 2016	Maximum 20 mg (5 mg in the morning, and 15 mg at bedtime) Mean dosage 15.6 ± 6.0 mg; mid-morning dosages of 4.0 ± 1.4 mg	Maximum dosages: 10 mg at bedtime, and 2 mg mid-morning, with achieved dosages approximately 50% of those in men
Raskind et al, ² 2013	5 mg in the morning, and 20 mg at bedtime Mean dosage: 4 mg in the morning, and 15.6 mg at bedtime	2 mg in the morning, and 10 mg at bedtime Mean dosage: 1.7 mg in the morning, and 7 mg at bedtime
Calohan et al, ³ 2010	Maximum 10 mg at bedtime Mean dosage: 4.1 mg at bedtime	Maximum 10 mg at bedtime Mean dosage: 4.1 mg at bedtime
Taylor et al, ⁴ 2008	Range 2 to 6 mg Mean dosage: 3.1 ± 1.3 mg/d	Range 2 to 6 mg Mean dosage: 3.1 ± 1.3 mg/d
Raskind et al, ⁵ 2007	13.3 ± 3 mg/d	13.3 ± 3 mg/d
Peskind et al, ⁶ 2003 ^b	2 to 4 mg at bedtime	
Raskind et al, ⁷ 2003	9.5 mg at bedtime	9.5 mg at bedtime
Raskind et al, ⁸ 2002	20 mg at bedtime Mean dosage: 9.6 ± 0.9 mg at bedtime	20 mg at bedtime Mean dosage: 9.6 ± 0.9 mg at bedtime
Taylor et al, ⁹ 2002	1 to 4 mg at bedtime	1 to 4 mg at bedtime
Raskind et al, ¹⁰ 2000	2 to 5 mg at bedtime	2 to 5 mg at bedtime

Note: It is interesting to note that how using low dosage of prazosin at bedtime gradually evolved in to using higher dosages and twice daily dosing

^aThe large Phase 3 study (N = 304) did not separate prazosin from placebo; possibly because of inadequate dosage and twice daily dosing not adequately control symptoms for 24 hours

^bOnly older men (mean age, 76 ± 2; range, 67 to 83) were included in this study

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