

Prazosin initiation and dose titration in a patient with posttraumatic stress disorder on concurrent carvedilol

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Abstract

One mechanism involved in the pathophysiology of posttraumatic stress disorder (PTSD) is increased noradrenergic stimulation. Prazosin, a commonly utilized treatment for PTSD nightmares, works to block noradrenergic stimulation of the alpha-1 adrenoceptor. Dual antagonism of this receptor would be expected to increase risk of adverse effects. Carvedilol has both alpha-1 adrenergic and nonselective beta-adrenoceptor antagonist activity. To our knowledge, there is no clinical guidance on use of prazosin in patients concomitantly prescribed carvedilol for hypertension. This case describes the successful titration of prazosin for PTSD symptoms in a 49-year-old male concurrently prescribed carvedilol for hypertension. This patient had a previous unsuccessful prazosin trial due to adverse effects. His second trial of prazosin was efficacious and well tolerated using individualized titration with close monitoring by mental health clinical pharmacy specialists in the pharmacist-managed prazosin titration clinic. This case details the importance of utilizing caution and close follow-up in prazosin dose titration in patients prescribed concomitant alpha-1 antagonists. This appears to be the first case report describing the successful dose titration of prazosin for PTSD in a patient on a concurrent alpha-1 antagonist antihypertensive agent.

Keywords: PTSD therapy, dual alpha antagonist, prazosin, nightmare

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Background

Posttraumatic stress disorder (PTSD) is defined as clusters of distressing symptoms associated with exposure to a traumatic event(s).¹ Symptoms can include recurrent and intrusive distressing memories or dreams of the event, psychosocial distress, hypervigilance, and irritability. The pathophysiology of PTSD is complex; research suggests² that the adrenergic system in PTSD may function with increased activity and lead to hyperarousal symptoms.

Prazosin is an alpha-1 adrenoceptor antagonist that crosses the blood-brain barrier and works to decrease postsynaptic noradrenergic activity.³ In multiple, smaller, randomized, controlled studies,⁴⁻⁹ prazosin has demonstrated efficacy in patients with PTSD, improving sleep quality while reducing nightmares. Despite these clinical recommendations regarding the role of prazosin, it remains utilized for the treatment of PTSD-related nightmares in the Veterans Affairs Health Care System (VAHCS).

The current literature lacks guidance regarding prazosin use for PTSD with coprescribed alpha-1 antagonist antihypertensive therapy. The VAHCS has utilized pharmacist-managed prazosin titration clinics (PMPTCs) to minimize the risk of adverse effects during prazosin titration in patients with a wide range of comorbidities. The clinician-administered PTSD scale nightmare frequency and intensity items, insomnia severity index, PTSD

TABLE 1: Rating scale scoring

Scale	Explanation
Posttraumatic Stress Disorder Checklist Scale	
0-10	No/minimal symptoms
11-20	Mild symptoms
21-40	Moderate symptoms
41-60	Sever symptoms
61-80	Very severe symptoms
Insomnia Severity Index	
0-7	No clinically significant insomnia
8-14	Subthreshold insomnia
15-21	Clinical insomnia (moderate)
22-28	Clinical insomnia (severe)
Clinically Administered Posttraumatic Stress Disorder Scale: Nightmare Frequency	
0	Never
1	Once/twice
2	1-2 times/wk
3	Several times/wk
4	Daily/almost daily
Clinically Administered Posttraumatic Stress Disorder Scale: Nightmare Intensity	
0	None
1	Mild/minimal distress, may not have awoken
2	Moderate, may have awoken in distress but can readily return to sleep
3	Severe, considerable distress, difficulty returning to sleep
4	Extreme, incapacitating distress, did not return to sleep

checklist can be utilized in PMPTCs to objectively monitor symptoms and guide dose titration (Table 1). This case describes successful initiation of prazosin in a patient with PTSD receiving dual-alpha antagonist therapy with carvedilol through the use of an individualized titration approach and close monitoring in a PMPTC.

Case Report

A 49-year-old white male with psychiatric history of PTSD, schizoaffective disorder, anxiety, and alcohol dependence (in remission) was referred to the PMPTC. At the time of referral, the patient denied use of alcohol, tobacco, or illicit substances. Medical history was significant for hypertension, headache, obstructive sleep apnea, diabetes mellitus type II, nephrolithiasis, and back pain. His antihypertensive regimen included carvedilol 3.125 mg twice daily, lisinopril 5 mg daily, and isosorbide mononitrate 30 mg daily for angina. His psychiatric medications included bupropion 1 mg 3 times daily, clonazepam 2 mg

twice daily, hydroxyzine 50 mg daily as needed for anxiety, lithium 600 mg twice daily, loxapine 5 mg in the morning and 20 mg in the evening, and venlafaxine extended-release 300 mg every morning.

The patient was diagnosed with PTSD in 2015 related to trauma sustained during his service in Operation Desert Storm. In 2016, he was trialed on prazosin 1 mg for nighttime PTSD symptoms. Per recommendation of cardiology service, beta blocker therapy was changed from carvedilol, an agent with selective alpha-1 blockade, to metoprolol tartrate 12.5 mg twice daily with selective beta-1 blockade to minimize intolerability with prazosin. One month after prazosin initiation, the patient presented to the emergency department with severe headache and dizziness and a blood pressure of 149/85 mmHg. Prazosin and metoprolol were discontinued, and carvedilol was reinitiated.

One year later, when he reported frequent nightmares to his mental health provider, he was referred to the PMPTC. At the initial visit, the patient reported no change to the medication regimen from the previous prazosin trial. Symptoms included poor sleep, nightmares 5 to 6 nights per week, restlessness throughout the night, and daytime hypervigilance and irritability. Baseline blood pressure readings were within goal range of 130/80 mmHg per American College of Cardiology and American Heart Association guidelines¹⁰ (Table 2), and his antihypertensive regimen was well tolerated. After discussing the risks and benefits of prazosin therapy, prazosin 1 mg was initiated at bedtime.

At his first follow-up visit on week 2, the patient reported improvement in sleep and restlessness. He also reported mild dizziness 1 hour after taking his nighttime dose, moderate dizziness in the morning following dose administration, and mild dizziness throughout the next day. Prazosin 1 mg was continued at bedtime for 5 weeks with improvements in clinically assessed measures (Table 2). Tolerable, intermittent dizziness was reported throughout the day; no objective signs of hypotension were reported.

The patient desired prazosin dose escalation to 2 mg at bedtime at week 6 to further target nightmare frequency and intensity. On this dose, he described a slight improvement in nightmare intensity (Table 2). After 2 weeks with good tolerability, prazosin was cautiously increased to 3 mg at bedtime with continued improvements in dizziness and PTSD symptoms and with no nightmares in more than 6 weeks (Table 2).

He maintained benefits with prazosin 3 mg for about 2 months. After 2 months, prazosin was increased to 4 mg at bedtime to target increased nightmares. He reported

TABLE 2: Summary of prazosin dosing, blood pressure (BP), reported clinician-administered posttraumatic stress disorder scale (CAPS) scores, sleep hours, sleep satisfaction, insomnia severity index (ISI; scale 1-28), and posttraumatic stress disorder checklist (PCL-5; scale 1-80) scores

Date, wk	Prazosin Dose, mg	BP, mmHg ^a	CAPS-Frequency	CAPS-Intensity	Average Sleep, h/wk	Sleep Satisfaction Score	ISI Score	PCL-5 Score
1 (baseline)	0	113/77	4	3	5-6	4 - very dissatisfied	19	54
2	1	140/93	4	3	6	2 - moderately satisfied		
4	1	142/92	3	2.5	6-7	2 - moderately satisfied		
6	2	114/78	2	2.5	10	2 - moderately satisfied	8	46
7	2	164/106	2	2.5	6-7	1 - satisfied		
8	2	150/98	3	1.5	7-8	1 - satisfied		
9	3	134/87	0	0	9	1 - satisfied		
10	3	146/98	0	0	8.5-9	1 - satisfied		
11	3	Not reported	0	0	9	1 - satisfied	9	45
13	3	137/91	0	0	9	0 - very satisfied		
21	3	138/85	3	3	6	2 - moderately satisfied	15	68
22	4	127/86	2	3	8			
23	4	139/88	1	0	4-5			
24	4	142/82	1	0	8			
27	4	156/90	0	0	6-7			
34	4	143/84	2	2	9			

^aBP was patient-measured through the Veterans Affairs Home Telehealth Reporting Service.

variability in frequency or intensity of nightmares and sleep hours in the context of ongoing psychosocial stressors (Table 2) but continued 4 mg with less frequent follow-up and no other medication changes. He continues to feel that the benefits of prazosin outweigh the risks and inconvenience of brief episodes of dizziness. Prazosin continues to be monitored at less frequent follow-up intervals to ensure sustained efficacy and tolerability.

Discussion

Literature review revealed no clinical guidance regarding prazosin use in PTSD with coprescribed antihypertensives with alpha-antagonist properties. However, the VAHCS does provide dosing recommendations for dual alpha-antagonist therapy in patients with benign prostatic hyperplasia and PTSD.¹¹ Therefore, many factors were considered during prazosin titration with the patient described in this case report. Our primary concern was increased risk of adverse events with concurrent carvedilol due to the dual alpha-1 antagonizing effects. Because of the patient's concomitant medications and comorbid medical conditions, the approach to prazosin titration was very gradual as compared to what may be commonly prescribed on an outpatient basis. However, because of the gradual titration and close follow-up offered by mental health clinical pharmacy specialists in the PMPTC, this veteran was able to successfully achieve positive outcomes while minimizing adverse events that may have

occurred without close monitoring on a more rapid titration schedule.

Orthostasis can be attributed to the pharmacologic properties of prazosin if used concomitantly with other antihypertensive medications. Prazosin has a higher affinity for the alpha-1 adrenoceptor compared to nonselective beta blockers with alpha blocking properties. Prazosin is reversibly but tightly bound to this receptor,^{12,13} whereas carvedilol has a higher affinity for beta-receptors compared to alpha-1 adrenoceptors. Therefore, the alpha-blocking effect is less apparent with carvedilol than prazosin.¹⁴

It is important to consider that other medications with alpha-antagonist properties may be prescribed in psychiatric patients. Antipsychotics with alpha-1 antagonism that carry a moderate-to-high risk for orthostasis include chlorpromazine, thioridazine, loxapine, clozapine, olanzapine, risperidone, paliperidone, and quetiapine.^{15,16} Antidepressants with significant presynaptic alpha-1 antagonism include trazodone and tricyclic antidepressants.^{15,16} Relative incidence of orthostasis based on reports from phase III trials reflect similar incidence with prazosin and nonselective beta blockers; the incidence may be less with trazodone but higher with antipsychotics and tricyclic amine antidepressants.¹⁷⁻²² The patient was also previously prescribed concomitant alpha-antagonist medications prior to prazosin initiation. Loxapine was

considered in prazosin titration as it carries a moderate-to-high risk of orthostasis.^{15,16}

A recommended titration strategy utilized in the outpatient VAHCS is to start prazosin 1 mg at bedtime and titrate by 1 mg every 3 to 7 days to a dose of at least 5 mg at bedtime.²³ Previously published studies^{4-9,24} report variable prazosin dosing in veterans with PTSD, ranging from 10 to 25 mg per day. However, dosing is patient-specific, and some patients may benefit from lower doses.^{4-9,24} Target doses of prazosin are reached when adequate symptom control is achieved with minimal side effects.

To minimize adverse effects during prazosin titration, some VAHCSs have utilized PMPTCs. These clinics allow frequent assessment of PTSD-related outcomes and adverse effects, which can benefit patients with complex medication regimens. In absence of clinical guidance regarding use of concomitant dual alpha-1 antagonist agents, clinical judgment, cautious dose titration, and frequent follow-up initially in weekly intervals should be exercised to achieve a patient-specific target dose of prazosin.

Educating patients on the risks of dual alpha blockade is essential in preventing further adverse outcomes from orthostasis. Strategies for minimizing orthostasis may include utilizing caution with positional changes, avoiding sudden movements, staying seated if dizziness occurs, maintaining adequate hydration, and use of stable supports. Other risks associated with alpha-antagonism that the clinician should educate and monitor include priapism, headache, weakness, and chest pain.¹⁶

A recent trial²⁴ reported prazosin failed to alleviate distressing dreams or improve of sleep quality in veterans with chronic PTSD. Significant limitations to this trial include a high placebo response rate and selection bias toward patients who were clinically stable with a lower baseline blood pressure, possibly indicating symptom severity with a lower likelihood to be improved with antiadrenergic treatment. The 2017 Veterans Affairs/Department of Defense PTSD clinical practice guidelines²⁵ lowered the recommendation for use of prazosin based on the results of this larger randomized controlled trial, despite the publication of 5 smaller, positive randomized controlled trials in PTSD management.⁴⁻⁹ The 2018 National Institute for Health and Care Excellence guidelines²⁶ state limited evidence for the efficacy of prazosin to support giving the medication a recommendation. Overall, guidelines cite that there is not consistent evidence for or against use of prazosin. It has been suggested that the collective body of evidence with prazosin in PTSD management maintains support of use

in certain subsets of patients, and the PMPTC continues to be utilized in the VAHCS.²⁴

Conclusion

This is the first case reported of successful prazosin initiation in a patient concomitantly prescribed carvedilol and demonstrates that concomitant carvedilol does not preclude use or titration of prazosin. Further study is warranted to establish clinical guidance in patients concomitantly prescribed dual alpha antagonist therapy.

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