Recurrent Priapism in a Military Veteran Receiving Treatment for PTSD

Rachel A. Mann, BA; Arvin K. George, MD†‡*

ABSTRACT Introduction: For veterans struggling with post-traumatic stress disorder (PTSD), symptomatic control often requires multiple psychotropic agents. We describe a case in which a young veteran experienced recurrent priapism while receiving treatment for PTSD with several medications, most notably trazodone and prazosin. Case Description: Our patient presented to the emergency department with priapism, approximately 3 months after beginning a pharmacologic regimen of escitalopram, prazosin, trazodone, and methylphenidate for PTSD. Detumescence was achieved, and he was instructed to discontinue trazodone. Approximately 1 month after discontinuation, he presented to the emergency department with recurrent priapism. Our patient had no obvious risk factors, including sickle cell disease, cocaine use, or utilization of phosphodiesterase type 5 inhibitors. After his second episode, our patient discontinued prazosin, and after 6 weeks had not experienced recurrence. Discussion: Food and Drug Administration-approved medications alone are often inadequate to treat-specific symptoms, especially those related to sleep. Consequently, trazodone and prazosin are frequently used off-label. Although priapism has been associated with these medications, there are currently no data available regarding the incidence of priapism related to dose or combination with other agents. Combat veterans may represent a population at higher risk for priapism given their often complex psychotropic regimens.

CASE REPORT

Our patient was a 29-year-old Iraq War veteran with a history of posttraumatic stress disorder (PTSD). He served in the U.S. Army for 11 years, and was deployed to Afghanistan where he was involved in extensive combat. Once he retired from the military, he began to experience nightmares and flashbacks related to his deployment. Before sleep, he would often hear the voices of his comrades repeatedly screaming his name. Over the next several months he endorsed feelings of hypervigilance; he avoided crowds and reminders of combat. He exhibited symptoms of depression, including low mood, anhedonia, and intractable irritability which on occasion manifested as physical aggression/violence. Throughout this time, our patient denied previous or current use of alcohol or any illicit substances. He first sought psychiatric assessment and management in 2013. He was treated with a number of psychotropic medications including valproic acid, prazosin, nortriptyline, buspirone, trazodone, modafinil, and duloxetine, although compliance with treatment was inconsistent. After 1 year without pharmacotherapy, our patient elected to restart psychotropic medications. He was initiated on a regimen of escitalopram, prazosin, and trazodone titrated to 20, 20, and 200 mg QD, respectively. Methylphenidate (10 mg QD) was added shortly thereafter for symptoms of fatigue and difficulty concentrating. Three months after the initiation of these medications, our patient presented to the emergency department with a painful erection that had persisted for nearly 7 hours. He had no risk factors for priapism, including cocaine abuse or sickle cell disease, and he denied use of phosphodiesterase type 5 inhibitors or alternative erectile aids, and his urine drug screen was negative. Detumescence was achieved with irrigation and aspiration including phenylephrine irrigation (750 mcg/5 cc) with a total of 50 cc in a monitored setting. He was discharged home after a period of observation without recurrence and was instructed to discontinue trazodone, as this was suspected to have precipitated his priapism. Approximately 1 month later, he presented to the emergency department with a duplicate presentation of priapism for 2 hours in duration. Detumescence was successfully achieved for the second time using irrigation and phenylephrine injection (300 mcg/5 cc) with a total of 50 cc. Urine drug screen was negative. Our patient was then instructed to discontinue prazosin and methylphenidate in the setting of recurrent priapism without a clear etiology. After 6 weeks of follow-up, our patient had not experienced any additional episodes of priapism, and had no residual sequelae.

DISCUSSION

Priapism, defined as a persistent, painful erection, is considered a urologic emergency.[1] There are two distinct forms of priapism-ischemic (low flow) and nonischemic (high flow). More than 95% of all cases of priapism are low flow, which carries a greater risk of complications such as erectile dysfunction, disfigurement, or in severe cases, penile necrosis.[2] Prompt resolution is indicated to avoid these clinical sequelae. The incidence of priapism in the population is low (0.5–0.9 cases per 100,000 person-years); however, several known risk factors have been identified.[3] These include

*University of Michigan Medical School, 1500 E. Medical Center Drive, Ann Arbor MI 48105.

†Department of Urology, University of Michigan, 1500 E. Medical Center Drive, Ann Arbor MI 48105.

‡VA Ann Arbor Healthcare System, 2215 Fuller Road, Ann Arbor, MI 48105.

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TABLE I. Medications Associated With Priapism

Medication Class	Examples
Vasoactive Erectile Agents	Papaverine, Phentolamine, Prostaglandin E1/Alprostadil
Alpha-Adrenergic Receptor Antagonists	Prazosin, Terazosin, Doxazosin, Tamsulosin
Antianxiety Agents	Hydroxyzine
Anticoagulants	Heparin, Warfarin
Antidepressants and Antipsychotics	Trazodone, Bupropion, Fluoxetine, Sertraline, Lithium, Clozapine, Risperidone, Olanzapine, Chlorpromazine, Thioridazine, Phenothiazines
Antihypertensives	Hydralazine, Guanethidine, Propranolol
Hormones	Gonadotropin-Releasing Hormone, Testosterone
Recreational Drugs	Alcohol, Marijuana, Cocaine

Reproduced from Salonia et al[3] European Association of Urology guidelines on priapism.

sickle cell anemia, leukemia, intracavernosal injection for erectile dysfunction, phosphodiesterase type 5 inhibitors, cocaine use, and many other medications including a number of psychotropic medications (Table I).[1–5] The association between trazodone use and priapism has been well documented for decades, but recently many other psychotropic medications have been found to share this risk.[6–8] Competitive antagonism of alpha-1 adrenergic receptors is thought to be responsible for interfering with the sympathetic control of penile detumescence.[9–12] Prazosin, an alpha-blocker traditionally used as an antihypertensive, has been increasingly used in the treatment of sleep-related disorders. Although large-scale data are lacking, the incidence of priapism associated with prazosin (or other similar alpha-blockers) has been documented in several small case studies.[13–16] Because of the lack of available data, incidence of priapism resulting from prazosin therapy is unknown. Nightmares and sleep disturbances are common among military veterans with PTSD.[17] Currently, only two selective serotonin reuptake inhibitors (SSRIs) are approved by the Food and Drug Administration for the treatment of PTSD.[18,19] Although SSRIs have been shown to improve mood and decrease anxiety, there is little evidence to support their efficacy for sleep related disorders.[17] As a result, medications such as trazodone and prazosin are often used off label for treatment of these symptoms.[20,21] These medications have proven to be effective and well tolerated in several trials, and are often used in combination with SSRIs or other psychotropic medications.[22–29] Depending on the severity of the symptoms, patients often require these medications to be titrated to high dose to achieve a therapeutic effect.[27] The relationship of trazodone dosage to priapism risk is largely unknown; however, a recent study demonstrated an increased risk of trazodone-induced priapism in the veteran population.[28] With regard to prazosin, the correlation between priapism risk and dosage remains unclear; this is largely the result of the limited number of documented cases. It could be inferred that titration of alpha-blocking agents to high doses may place patients at a higher risk of priapism; however sufficient data are lacking to demonstrate this association. Unfortunately, rates of PTSD and major depression in military veterans returning from combat is staggering, and ranges from 9% to 31% depending on the specific functional markers measured.[30,31] Combat veterans who fought in Iraq, such as our patient, had higher reported rates of PTSD than those deployed to other countries.[32] In addition to emotional distress, veterans suffering from PTSD are more likely to be unemployed, have additional medical comorbidities, and higher rates of military attrition.[33,34] Multimodal treatment with cognitive behavioral therapy (CBT) and SSRIs is considered the most effective treatment option for PTSD, but pharmacotherapy alone has become a mainstay of treatment.[35–40] The numerous barriers to psychiatric care, including lack of provider availability, time commitment, and perceived social stigma of psychotherapy, are likely contributing factors to the underutilization of CBT in veterans suffering from PTSD.[41–43] Although CBT has shown to be more effective than any pharmacologic agent alone, attending weekly sessions for 12 weeks may be impractical for those who continue to work.[44–50] Pharmacotherapy is significantly less time consuming, may be managed by a multitude of health care providers, and perhaps most importantly, allows veterans to maintain a higher level of anonymity. Regardless of the modality, it is universally accepted that patients with PTSD must be effectively treated in an effort to restore function and quality of life. The prevalence, severity, and stigma related to psychiatric disorders in the veteran population illuminates unique challenges when choosing therapy. Although priapism is typically regarded as a rare side effect of psychotropic medications, the frequent use of trazodone and prazosin in combat veterans may place these patients at higher risk than the general population. Additionally, synergistic effects with multiple drug combinations are unknown. Since large scale data regarding the incidence of priapism in these patients are lacking, it is important that clinicians remain aware of this risk when treating veterans, and are able to educate patients regarding this potentially debilitating side effect. Furthermore, alternative treatments such as CBT should be considered if symptoms are refractory to several psychotropic agents. The underutilization of psychotherapy in these patients further illustrates the need for mental health reform in an effort to increase access to services, and decrease the stigma associated with PTSD in military culture.

REFERENCES

1. Montague DK, Jarow J, Broderick GA, et al: American Urological Association guideline on the management of priapism. J Urol 2003; 170(4 Pt 1): 1318–24.
2. Broderick GA, Kadioglu A, Bivalacqua TJ, et al: Priapism: pathogenesis, epidemiology, and management. J Sex Med 2010; 7(1 Pt 2): 476–500.

3. Salonia A, Eardley I, Giuliano F, et al: European Association of Urology guidelines on priapism. Eur Urol 2014; 65(2): 480–9.
4. Eland IA, Van Der Lei J, Stricker BH, et al: Incidence of priapism in the general population. Urology 2001; 57(5): 970–2.
5. Winter CC, McDowell G: Experience with 105 patients with priapism: update review of all aspects. J Urol 1988; 140(5): 980–3.
6. Sood S, James W, Bailon MJ: Priapism associated with atypical antipsychotic medications: a review. Int Clin Psychopharmacol 2008; 23(1): 9–17.
7. Armstrong WR, Grimsby GM, Jacobs MA: Pediatric priapism secondary to psychotherapeutic medications. Urology 2015; 86(2): 376–8.
8. Brichart N, Delavierre D, Peneau M, et al: Priapism associated with antipsychotic medications: a series of four patients. Prog Urol 2008; 18(10): 669–73.
9. Thompson JW Jr, Ware MR, Blashfield RK: Psychotropic medication and priapism: a comprehensive review. J Clin Psychiatry 1990; 51(10): 430–3.
10. Carruthers SG: Adverse effects of alpha 1-adrenergic blocking drug. Drug Saf 1994; 11(1): 12–20.
11. Saenz de Tejada I, Ware JC, Blanco R, et al: Pathophysiology of prolonged penile erection associated with trazodone use. J Urol 1991; 145(1): 60–4.
12. Andersohn F, Schmedt N, Weinmann S, et al: Priapism associated with antipsychotics: role of alpha-1 adrenoceptor affinity. J Clin Psychopharmacol 2010; 30(1): 68–71.
13. Sadeghi-Nejad H, Jackson I: New-onset priapism associated with ingestion of terazosin in an otherwise healthy man. J Sex Med 2007; 4(6): 1766–8.
14. Nakamura N, Takaesu N, Arakaki Y: Priapism in haemodialysis patients due to prazosin? Br J Urol 1991; 68(5): 551–2.
15. Mandel LR: Priapism secondary to prazosin therapy. Mil Med 1987; 152(10): 523–4.
16. Bullock N: Prazosin-induced priapism. Br J Urol 1988; 62(5): 487–8.
17. George KC, Kebejian L, Ruth LJ, et al. Meta-analysis of the efficacy and safety of prazosin versus placebo for the treatment of nightmares and sleep disturbances in adults with posttraumatic stress disorder. J Trauma Dissociation 2016; 17(4): 494–510.
18. Brady K, Pearlstein T, Asnis GM, et al. Efficacy and safety of sertraline treatment of posttraumatic stress disorder: a randomized controlled trial. JAMA 2000; 283(14): 1837–44.
19. Marshall RD, Beebe KL, Oldham M, et al: Efficacy and safety of paroxetine treatment for chronic PTSD: A fixed-dose, placebo-controlled study. Am J Psych 2001; 158(12): 1982–8.
20. Department of Veterans Affairs: Clinician's Guide to Medications for PTSD. Washington, DC, Veterans Health Administration, 2016. Available at http://www.ptsd.va.gov/professional/treatment/overview/cliniciansguide-to-medications-for-ptsd; accessed on October 28, 2016.
21. Bossini L, Coluccia A, Casolaro I, et al: Off-label trazodone prescription: evidence, benefits and risks. Curr Pharm Des 2015; 21(23): 3343–51.
22. Smith C, Koola MM: Evidence for using doxazosin in the treatment of posttraumatic stress disorder. Psychiatr Ann 2016; 46(9): 553–5.
23. Walsh JK, Erman M, Erwin CW: Subjective hypnotic efficacy of trazodone and zolpidem in DSMIII-R primary insomnia. Hum Psychopharmacol Clin Exp 1998; 13: 191–8.
24. Khachatryan D, Groll D, Booji L, et al: Prazosin for treating sleep disturbances in adults with posttraumatic stress disorder: a systematic review and meta-analysis of randomized controlled trials. Gen Hosp Psychiatry 2016; 39: 46–52.
25. Raskind MA, Peskind ER, Kanter ED, et al: Reduction of nightmares and other PTSD symptoms in combat veterans by prazosin: a placebo-controlled study. Am J Psych 2003; 160(2): 371–3.
26. Raskind MA, Thompson C, Petrie EC, et al. Prazosin reduces nightmares in combat veterans with posttraumatic stress disorder. J Clin Psychiatry 2002; 63(7): 565–8.
27. Raskind MA, Peterson K, Williams T, et al: A trial of prazosin for combat trauma PTSD with nightmare in active-duty soldiers returned from Iraq and Afghanistan. Am J Psych 2013; 170(9); 1003–10.
28. Warner MD, Dorn MR, Peabody CA: Survey on the usefulness of trazodone in patients with PTSD with insomnia or nightmares. Pharmacopsychiatry 2001; 34(4): 128–31.
29. Singareddy RK, Balon R: Sleep in posttraumatic stress disorder. Ann Clin Psychiatry 2002; 14(3): 183–90.
30. Thomas JL, Wilk JE, Riviere LA, et al: Prevalence of mental health problems and functional impairment among active component and National Guard soldiers 3 and 12 months following combat in Iraq. Arch Gen Psychiatry 2010; 67: 614–23.
31. Crum-Cianflone NF, Powell TM, LeardMann CA, et al: Mental health and comorbidities in U.S. military members. Mil Med 2016; 181(6): 537–45.
32. Hoge CW, Castro CA, Messer SC, et al: Combat duty in Iraq and Afghanistan, mental health problems and barriers to care. US Army Med Dep J 2008; Jul-Sep: 7–17.
33. Hoge CW, Auchterlonie JL, Milliken CS: Mental health problems, use of mental health services, and attrition from military service after returning from deployment to Iraq or Afghanistan. JAMA 2006; 295(9): 1023–32.
34. Smith TC, Wingard DL, Ryan MA, et al: Millennium Cohort Study Team: PTSD prevalence, associated exposures, and functional health outcomes in a large, population-based military cohort. Public Health Rep 2009; 124(1): 90–102.
35. Jakupcak M, Cook J, Imel Z, et al: Posttraumatic stress disorder as a risk factor for suicidal ideation in Iraq and Afghanistan War veterans. J Trauma Stress 2009; 22(4): 303–6.
36. Kang HK, Bullman TA: Risk of suicide among US veterans after returning from the Iraq or Afghanistan war zones. JAMA 2008; 13l300(6): 652–3.
37. LeardMann CA, Powell TM, Smith TC, et al: Risk factors associated with suicide in current and former US military personnel. JAMA 2013; 310(5): 496–506.
38. Reisman M: PTST treatment for veterans: what's working, what's new, and what's next. PT. 2016; 41(10): 623–27,632–34.
39. Forbes D, Creamer M, Bisson JI, et al: A guide to guidelines for the treatment of PTSD and related conditions. J Trauma Stress 2010; 23: 537–552.
40. Cuijpers P, Sijbrandij M, Koole SL, et al: Adding psychotherapy to antidepressant medication in depression and anxiety disorders: a meta-analysis. World Psychiatry 2014; 13: 56–67.
41. U.S. Department of Veterans Affairs: Access Audit System-Wide Review of Access (May 12, 2014–June 3, 2014). Available at www.va.gov/health/docs/VAAccessAuditFindingsReport.pdf; accessed May 17, 2017.
42. Corrigan P. How stigma interferes with mental health care. Am Psychol 2004; 59: 614–25.
43. Committee on the Assessment of the Readjustment Needs of Military Personnel, Veterans, and Their Families, Board on the Health of Select Populations, Institute of Medicine. Returning Home from Iraq and Afghanistan: Assessment of Readjustment Needs of Veterans, Service Members, and Their Families. Washington, DC, National Academies Press, 2013. Available at www.nap.edu/read/13499/chapter/1. Accessed May 17, 2017.
44. U.S. Department of Veterans Affairs. Prolonged exposure therapy. Aug 14, 2015. Available at www.ptsd.va.gov/public/treatment/therapy-med/prolonged-exposure-therapy.asp; accessed May 17, 2017.
45. U.S. Department of Veterans Affairs. Cognitive Processing Therapy. Aug 14, 2015. Available at www.ptsd.va.gov/public/treatment/therapy-med/cognitive_processing_therapy.asp; accessed May 17, 2017.
46. Walter KH, Varkovitzky RL, Owens GP, et al: Cognitive processing therapy for veterans with posttraumatic stress disorder: a comparison between outpatient and residential treatment. J Consult Clin Psychol 2014; 82(4): 551–61.

47. Dickstein BD, Walter KH, Schumm JA, et al: Comparing response to cognitive processing therapy in military veterans with subthreshold and threshold posttraumatic stress disorder. J Trauma Stress 2013; 26(6): 703–9.
48. Morland LA, Mackintosh MA, Greene CJ, et al: Cognitive processing therapy for posttraumatic stress disorder delivered to rural veterans via telemental health: a randomized noninferiority clinical trial. J Clin Psychiatry 2014; 75(5): 470–6.
49. Monson CM, Schnurr PP, Resick PA, et al: Cognitive processing therapy for veterans with military-related posttraumatic stress disorder. J Consult Clin Psychol 2006; 74(5): 898–907.
50. Foa EB, Gillihan SJ, Bryant RA: Challenges and successes in dissemination of evidence-based treatments for posttraumatic stress: lessons learned from prolonged exposure therapy for PTSD. Psychol Sci Public Interest 2013; 14(2): 65–111.