High-dose prazosin for the treatment of post-traumatic stress disorder

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Ther Adv Psychopharmacol

2014, Vol. 4(1) 43–47

DOI: 10.1177/2045125313500982

Abstract: Patients with post-traumatic stress disorder (PTSD) are frequently symptomatic despite being on medications currently approved by the US Food and Drug Administration for PTSD. There is evidence to support the notion that prazosin is effective for PTSD nightmares. However, PTSD-related nightmares often do not resolve completely on a low dose of prazosin. The capacity of prazosin to treat daytime symptoms of PTSD which are distressing to patients has not been well studied. Clinicians are reluctant to increase the dose of prazosin due to side effect concerns. To date, the highest reported dose of prazosin used for PTSD is 16 mg daily. We illustrate two case reports using high-dose (up to 30 and 45 mg) prazosin for PTSD with comorbid treatment-resistant mood disorders. We report that high-dose prazosin was safe, tolerable and effective for PTSD in adults. To our knowledge, this is the first case series to highlight the importance of using high-dose prazosin for the treatment of PTSD. In patients with partial response to currently available medications for PTSD, greater utilization of high-dose prazosin for the management of PTSD may lead to better outcomes.

Keywords: High dose prazosin, post-traumatic stress disorder, comorbid depression

Introduction

Patients with post-traumatic stress disorder (PTSD) are frequently symptomatic despite being medications currently approved by the US Food and Drug Administration for PTSD. There is evidence to support the notion that prazosin is effective for PTSD nightmares. However, PTSD-related nightmares often do not resolve completely on a low dose of prazosin. The capacity of prazosin to treat daytime symptoms of PTSD which are distressing to patients has not been well studied.

To date, the highest reported dose of prazosin used for PTSD is 16 mg daily. In a study entitled 'A Double-blind Placebo-controlled Trial of Prazosin for the Treatment of Alcohol Dependence', the maximum dose was 16 mg which was achieved during a 2-week titration. Prazosin 16 mg was well tolerated and beneficial for pharmacologic treatment of alcohol dependence [Simpson *et al.* 2009]. In a systematic review of 21 studies, consisting of four randomized controlled trials, four open-label studies, four retrospective chart reviews and nine case reports, the prazosin dose ranged from 1 to 16 mg daily. Overall, the studies showed that patients were able to tolerate 16 mg daily with dizziness as a common adverse effect. This systematic review found a small but positive evidence base to support the efficacy of prazosin therapy for nightmares. One of the objectives of this systematic review was to identify evidence for the use of prazosin to treat non-PTSD-related nightmares and they were not able to find any evidence to support it. However, there were several recent narratives of the use of prazosin to treat PTSD-related nightmares. The authors concluded that prasozin is a well tolerated generically available medication that has a small but positive evidence base for the treatment of PTSD-associated nightmares [Kung *et al.* 2012]. There are several ongoing clinical trials on high-dose prazosin use for PTSD (clinicaltrials.gov). In the randomized, double-blind trial 'Prazosin and Combat Trauma in PTSD', the prazosin maximum dose is 20 mg daily. In another study, 'Efficacy of Adjunct Sleep Interventions for PTSD', the maximum dose of prazosin is 15 mg daily. In 'Prazosin for Noncombat Trauma PTSD', the maximum dose used is 25 mg daily. The highest dose of prazosin used clinically is 50 mg daily

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in veterans with PTSD and with no side effects (Raskind 2009, personal communication).

Prazosin

Prazosin is an α1 adrenoreceptor antagonist; it is nonsedating and blocks excessive responsiveness to norepinephrine stimulation at postsynaptic α1 adrenergic receptor. Following oral administration, human plasma concentrations reach a peak at about 3 h with a plasma half life of 2–3 h. The drug is highly bound to plasma protein. Animal studies indicate that prazosin is extensively metabolized, primarily by demethylation and conjugation, and excreted mainly via bile and feces. The maximum dose recommended in the prazosin package insert (PI) is 40 mg daily.

The most important adverse effect is the 'first dose effect' syncope with sudden loss of consciousness (1%) with an initial dose of at least 2 mg. Hence, prazosin should always be started at 1 mg. Some of the common side effects of prazosin are the following: dizziness (10%), headache (8%), drowsiness (8%), lack of energy (7%), weakness (7%), palpitations (5%) and nausea (5%). In 1–4% of patients taking prazosin the following side effects have been reported: vomiting, diarrhea, constipation, edema, orthostatic hypotension, dyspnea, syncope, vertigo, depression, nervousness, rash, urinary frequency and nasal congestion. In less than 1% of patients taking prazosin, abdominal discomfort/pain, tachy cardia, paresthesias, hallucinations, pruritus, incontinence, impotence and priapism have been reported (PI).

We illustrate two case reports using high-dose (up to 30 and 45 mg) prazosin for PTSD with comorbid treatment-resistant mood disorders. In patients with partial response to currently available medications for PTSD, greater utilization of high-dose prazosin for the management of PTSD may lead to better outcomes.

Case 1

A 50-year-old Hispanic woman with major depressive disorder (MDD), recurrent, severe with a history of seasonal component and PTSD was referred to the treatment-resistant affective disorders (TRAD) clinic. She was on mirtazapine 45 mg daily, sertraline 200 mg daily and diazepam 5 mg four times daily, all taken orally. The psychotropic drug history showed that lorazepam, hydroxyzine 75 mg and duloxetine (dose unknown) were not effective in the past. Considering the patient's past hypomanic episodes (approximately 30 hypomanic episodes in the past 30 years, each lasting 2 days to 2 weeks), coupled with depressive episodes, the patient's diagnosis was changed to bipolar II.

At the time of presentation, the patient completed the Patient Health Questionnaire 9 (PHQ-9), a nine-item scale used to screen for depression [Kroenke *et al.* 2001]. The patient scored 23 on the PHQ-9 and reported her functioning as 'extremely difficult'. The patient was physically and sexually abused as a child and as an adult. The patient endorsed nightmares and daytime symptoms such as hyperarousal, flashbacks and re-experiencing the trauma. PTSD symptoms were chronic and active for many years.

Mirtazapine and sertraline were tapered and discontinued because of the new bipolar II diagnosis [Sachs *et al.* 2007; Salvi *et al.* 2008; Alda and Yatham, 2009] and diazepam was tapered and discontinued as the patient had PTSD which was symptomatic [Asnis *et al.* 2004; Lund *et al.* 2012]. For PTSD, she was started on an oral dose of 1 mg prazosin at bedtime [Peskind *et al.* 2003]. Prazosin was gradually titrated based on response over 20 weeks to 15 mg in the morning, 10 mg at noon and 20 mg at night. The patient did not report any side effects from this high dose of prazosin. Morning and noon doses were specifically to target daytime symptoms and the bedtime dose to target nightmares. Each time prazosin was increased by 2 mg daily to target a specific daytime or nighttime symptom. In this patient, daytime symptoms were more distressing than nightmares and hence this patient required 25 mg prazosin during the daytime and 20 mg at bedtime. On prasozin 45 mg, the patient reported almost complete remission (90% improvement according to the patient clinically), including daytime symptoms such as hyperarousal, flashbacks and daytime re-experiencing of the trauma and nightmares. For insomnia, daytime doses of prazosin were switched to 13 mg in the morning, 8 mg at noon and 24 mg at bedtime. Not only did this fail to improve insomnia but the patient also started to re-experience daytime PTSD symptoms. The baseline blood pressure (BP) and heart rate (HR) were 120/56 (sitting), 105/70 (standing), 73 (sitting), 71 (standing). The patient's BP and HR on prazosin were 102/72 (sitting), 100/70 (standing), 80 (sitting) and 88 (standing). In addition, the patient was also on lisinopril 10 mg

daily and *hydrochlorothiazide* 50 mg daily, both taken orally. Orthostasis is defined as a decrease in systolic BP by more than 20 mmHg or a decrease in diastolic BP by more than 10 mmHg or a pulse increase of more than 10 beats/min. This patient, despite being on a high dose of prazosin and two other antihypertensives, did not have orthostasis or any other symptoms associated with it.

Comorbid bipolar depression was managed with a rational combination therapy: lamotrigine 200 mg at bedtime, melatonin 6 mg at bedtime, mirtazapine 45 mg at bedtime, pramipexole 4 mg at bedtime [Aiken, 2007], methylphenidate [Candy *et al.* 2008] 20 mg in the morning and 20 mg at noon (use of methylphenidate for short-term treatment of bipolar depression should be considered aggressive) and zolpidem 15 mg at bedtime. Lamotrigine was chosen [Yatham *et al.* 2009; Koola *et al.* 2011] over lithium for bipolar depression and because she had psoriasis and diabetes mellitus. In addition, she was on angiotensin-converting enzyme inhibitor (for hypertension) and likely to take nonsteroidal anti-inflammatory drugs for arthritis. Quetiapine was not considered because of the risk of metabolic syndrome including obesity. For behavioral activation, the patient was asked to paint things she enjoyed in the past when she was not depressed. After three and a half months, the patient's PHQ-9 decreased from 23 (initial presentation) to 8.

With the above-mentioned treatments, the patient's functioning improved in the following areas: able to focus better, doing a variety of things instead of just hibernating, improved memory, clear thinking, enjoying time with her granddaughter, working more in the flower garden and she could travel alone. The patient was followed for 1 year by the treatment team.

Case 2

A 46-year-old Hispanic woman with MDD, treatment-resistant depression (TRD) stage II, PTSD and panic disorder was referred to the TRAD clinic. TRD stages are the following: stage I: failure of at least one adequate trial of a major class of antidepressants; stage II: stage I resistance plus failure of an adequate trial of an antidepressant (or combination) in a distinctly different class from that used in stage I [Thase and Rush, 1997]. The following medications failed to provide benefit: paroxetine (dose unknown), venlafaxine 262.5 mg, duloxetine 60 mg daily, gabapentin 600 mg at bedtime, propranolol 10 mg three times a day, trazodone (dose unknown), prazosin 3 mg (which was discontinued because the patient was not able to tolerate it due to side effects), chlorpromazine 100 mg at bedtime, dextroamphetamine extended release 5 mg, risperidone 2 mg, aripiprazole 15 mg and lithium 900 mg. The patient came to us on clonazepam 2 mg twice a day, mirtazapine 45 mg at bedtime and zolpidem 20 mg at bedtime, all taken orally.

The patient scored 27 on PHQ-9, which is suggestive of severe depression. The patient's 1-year-old son had died and she was still grieving after 24 years. The patient's PTSD was from adult physical and sexual abuse, including rape. PTSD symptoms were flashbacks, hypervigilance, reliving the experience, avoidance, nightmares, insomnia and concentration difficulties. PTSD symptoms were chronic and active for many years. Prazosin was started at 1 mg orally at bedtime and was gradually titrated over 4 weeks to 15 mg in the morning, 5 mg at noon and 10 mg at bedtime based on response. Morning and noon doses were specifically to target daytime symptoms and the bedtime dose to target nightmares. Each time prazosin was increased by 2 mg daily to target a specific daytime or nighttime symptom. In this patient, daytime symptoms were more pronounced than the nightmares and hence required 20 mg during the daytime and 10 mg at bedtime. The patient tolerated prazosin without reporting any side effects. Her baseline sitting BP was 133/106 and standing BP was 132/104, sitting HR was 75 and standing HR was 78. On prazosin 30 mg, sitting BP was 124/85, standing BP was 121/95, sitting HR was 83 and standing HR was 86.

For the management of comorbid TRD, mirtazapine, zolpidem and clonazepam were tapered and discontinued. The patient was started on clomipramine because of TRD stage II. The patient was asked to continue psychotherapy and was referred for bereavement counseling. The patient was asked to start walking for 5 min daily for behavioral activation and gradually to increase the duration. The patient also attended the weekly depression/bipolar/psychosis group.

Two months later, the patient's PHQ-9 was 0 and her PTSD was asymptomatic on clomipramine 300 mg orally daily and prazosin 15 mg in the morning, 5 mg at noon and 10 mg at bedtime. It is unclear what specific side effects the patient had on

prazosin 3 mg when it was tried for the first time. It is also unknown what the starting dose was then and how quickly it was titrated. Also, we do not know what other medications she was on at that time. Prazosin should always be started at 1 mg at bedtime. Reassurance, conveying optimism, gradual titration and a quick response may have helped the patient to persist with prazosin. She may also have experienced improvement in PTSD symptoms on clomipramine.

The patient's functioning improved in the following domains: she started to think clearly; started to drive on the freeway (no phobia of death from an accident); was able to get out of bed during the daytime; had more interest in her appearance (personal hygiene); made more public appearances; developed a routine; started to belly laugh; started to enjoy family and friends; took up exercise and quit smoking. This patient was followed for 8 months and continued to maintain recovery.

One limitation of this case series is that PTSD symptoms were assessed and monitored using the *Diagnostic and Statistical Manual of Mental Disorders*, fourth edition, text revision criteria and not using a formal rating scale.

Implications for clinical care

Although in these cases no untoward side effects occurred, prazosin could be intolerable in some patients. In such cases, prazosin may have to be very gradually titrated, other antihypertensives can be discontinued or dose decreased after consulting with primary care physicians. The most common intolerable side effect from prazosin is dizziness and patients can be educated about this. Patients should be advised to monitor their BP with orthostatic changes at home and skip a dose if needed when they have side effects. Use of high-dose prazosin may be more difficult in patients with baseline low BP and the dosing may have to be done more cautiously. In this case series, both patients were women and could tolerate prazosin 30 and 45 mg. Women have a lower BP and more orthostasis than men. Hence, a higher dose than 30–45 mg may be tolerated and safely used in men.

In summary, in this case series, high-dose prazosin may have played an important role in the improvement of PTSD symptoms reported clinically in conjunction with improvement in comorbid depression and anxiety symptoms with rational combination therapy. The biggest challenge for clinicians is to determine what symptoms each patient has and how to divide the dose of prazosin accordingly to effectively manage both daytime and nighttime symptoms. The dose escalation of prazosin should be based on an individual patient's response and side effects. This approach may be of practical utility for clinicians which may lead to better outcomes.

Acknowledgements

Jan A. Fawcett, MD was the supervisor of Maju Koola, MD, the treating psychiatrist. We acknowledge Murray Raskind, MD for giving us information on prazosin. MMK and SPV contributed equally with the manuscript preparation and are joint first authors.

Funding

Maju Koola was supported by the American Psychiatric Association/Kempf Fund Award for Research Development in Psychobiological Psychiatry.

Conflict of interest statement

The authors declare no conflict of interest in preparing this article.

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