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Evidence for Using Doxazosin in the Treatment of Posttraumatic Stress Disorder

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Abstract

There is evidence that doxazosin is effective in the treatment of posttraumatic stress disorder (PTSD). Doxazosin is a “me-too” drug of prazosin. Doxazosin has an improved absorption profile and this likely minimizes the risk for unintended adverse hypotensive effects. The availability of doxazosin in the gastrointestinal therapeutic system (GITS) form permits a higher initial daily dose (4 mg/day) while avoiding significant first-dose side effects. The treatment of PTSD with prazosin has several disadvantages due to its short duration of action (6–8 hours), which results in multiple doses being required. Prazosin may wear off and this may lead to nightmares in the latter half of the sleep. Doxazosin has significant advantages over prazosin in clinical practice because it has a long half-life and requires only once-daily dosing. This may lead to better adherence and greater effectiveness in the treatment of PTSD.

The treatment of posttraumatic stress disorder (PTSD) with prazosin has several disadvantages.[1,2] Because it has a half-life of only 2 to 3 hours and a duration of action of 6 to 10 hours, multiple daytime doses are required. The beneficial effects of prazosin may wear off after 2 to 3 hours, which may lead to nightmares in the latter half of regular sleep. The daytime doses of prazosin can be tailored to a lower level than the nighttime doses to avoid occasional lethargy and other adverse effects. Prazosin requires dosing 2 to 4 times a day, which can lead to less adherence, resulting in less effectiveness. In contrast to prazosin, the “me-too” medication doxazosin has a half-life of 16 to 30 hours and, therefore, can be taken once daily with no extra daytime dosing required.[3] In contrast to prazosin, doxazosin has an improved absorption profile, which likely minimizes the risk for hypotension. Doxazosin administered via a gastrointestinal therapeutic system (GITS) permits a higher initial daily dose (4 mg/day) while avoiding the significant side effects of the initial dose.[3] Doxazosin dosed once daily (in the morning or at bedtime) has significant advantages over prazosin in clinical practice.[4,5] A comparison of side effects of doxazosin and prazosin is shown in Table 1.

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EVIDENCE FOR USE OF DOXAZOSIN IN PTSD

In a case report by Sethi and Vasudeva,[4] a 59-year-old combat veteran with PTSD, after 8 weeks of 4 mg/day of doxazosin, had improved sleep quality, decreased frequency and intensity of trauma-related nightmares, and improved ability to function during the daytime. In a 12-week open-label study with 12 participants with PTSD by De Jong et al.,[5] symptoms were significantly better on 4 to 8 mg/day of doxazosin. In a double-blind, placebo-controlled study in 8 participants with PTSD, doxazosin extended release [XL] GITS was titrated from 4 mg daily to 16 mg daily over the course of 12 days. After 4 days of treatment with 16 mg/day of doxazosin, there was a significant improvement in PTSD symptoms.[6] In a retrospective chart review of patients with PTSD,[7] 51 received treatment with doxazosin. Forty-six of the 51 patients continued doxazosin for 12 weeks, and there was a significant decrease in nightmares within the 12-week period. Approximately 25% of these patients treated for the 12-week course experienced full remission. It was also noted that sleep recuperation improved within the first 4 weeks of treatment with doxazosin.

In a large, phase 3 randomized clinical trial (RCT) of 304 participants, prazosin was not significantly better than placebo for PTSD.[8] This is despite men and women receiving 20 mg and 12 mg daily, respectively, for 26 weeks. An adequate treatment trial for PTSD is 8 to 15 weeks, therefore, one can assume that the dose was inadequate in this study.[8] Moreover, prazosin was dosed only twice daily in the study, which may not have completely treated all the PTSD symptoms throughout the day and nightmares at night (due to its short half-life). Despite this negative study, it does not change our practice of prescribing prazosin for PTSD. Doxazosin is a “me-too” medication of prazosin. Doxazosin is already extensively used in clinical practice to treat PTSD (Jan Fawcett, MD; Thomas Newton, MD; Anne Richards, MD; Christopher Rodgman, MD; written communication, 2015).

There is evidence to suggest that a high dose of prazosin is safe and effective in the treatment of PTSD.[9] Considering Raskind et al.’s[8] negative study, some patients may require higher doses of alpha-1 blockers for treatment-resistant PTSD. Doxazosin at 48 mg/day has been safely and effectively used in a patient to treat PTSD (Smith and Koola, unpublished data). There is evidence to use the combination of prazosin and doxazosin[10] (Smith and Koola, unpublished data). Prazosin is the most lipophilic of all the alpha-1 blockers. In 73 patients, pretreatment with doxazosin up to 56 mg was safely and effectively used for hemodynamic instability during surgery for pheochromocytoma.[11]

Patients may be on a regimen such as prazosin 1 mg in the morning, 1 mg at noon or early afternoon, and 5 mg at bedtime; or 3 mg in the morning, 2 mg at noon or early afternoon, and 4 mg at bedtime; or 5 mg in the morning, 2 mg at noon or early afternoon, and 5 mg at bedtime. It may be difficult for the physician to write the prescription and place the order if they are on the inpatient unit. Pharmacists sometimes ask for two prescriptions at times and they find it difficult to fill because of the number of pills they have to dispense and the various doses. It is difficult for patients to remember what dose they are taking and when to take it. Prazosin 1 mg in the morning, 1 mg at noon or early afternoon, and 5 mg at bedtime; 3 mg in the morning, 2 mg at noon or early afternoon, and 4 mg at bedtime; or 5 mg in the morning, 2 mg at noon or early afternoon, and 5 mg at bedtime may be approximately

equivalent to doxazosin 7 mg, 9 mg, and 12 mg daily, respectively. This is a simpler regimen for patients to remember and easy to use. The cost of doxazosin is almost the same as prazosin. Among all the alpha-1 adrenoreceptor antagonists (alfuzosin, doxazosin, prazosin, tamsulosin, terazosin), doxazosin has the longest half-life.

CONCLUSION

Doxazosin for the treatment of PTSD should be considered because it can lead to better adherence and greater effectiveness. These are some of the pragmatic reasons why doxazosin may be a better choice than prazosin to treat patients with PTSD.

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TABLE 1

Comparison of the Adverse Effects of Doxazosin and Prazosin[a]

Adverse Effect	Doxazosin (%)	Prazosin (%)
Dizziness	19	10
Headache	14	8
Drowsiness	5	8
Edema	4	1–4
Vertigo	2	1–4
Nervousness	2	<1
Impotence	2	<1
Palpitations	1.5	5
Nausea	1.2	5
Anxiety	1.1	1–4
Hypotension	1	1–4
Pruritis	1	<1
Rash	1	1–4
Depression	1	1–4
Paresthesias	1	1–4
Urinary frequency	<.5	1–4
Nasal congestion	<.5	1–4
Hallucination	<.5	1–4
Vomiting	<.5	1–4
Priapism	<.5	<1
Incontinence	<.5	<1
Tachycardia	<.5	<1

[a]Table is arranged in descending order of the adverse effects of doxazosin.

Data from package inserts.[12,13]