

Case report

Slow-release prazosin for SSRI-resistant posttraumatic stress disorder patients

Prazosina de liberação lenta para pacientes com transtorno do estresse pós-traumático resistentes aos ISRS

LUIZ FELIPE PAGOTTO¹, WILLIAM BERGER², MAURO VITOR MENDLOWICZ², MARIANA PIRES LUZ¹, CARLA MARQUES PORTELLA¹, IVAN FIGUEIRA¹

¹Instituto de Psiquiatria da Universidade Federal do Rio de Janeiro (IPUB/UFRJ).

²Universidade Federal Fluminense (UFF).

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Abstract

Background: Prazosin is an antagonist of alpha-1 adrenergic receptor used to treat PTSD-related nightmares and insomnia. Although evidence suggests that it is also effective in the treatment of general symptoms of PTSD, its short half-life (2-3 hours) may limit its therapeutic effects. **Objective:** To describe four cases of patients with PTSD resistant to selective serotonin reuptake inhibitors (SSRIs) or selective serotonin/noradrenaline reuptake inhibitor (SNRIs) therapy (conventional therapy) treated with slow-release prazosin presentation. **Methods:** Four patients with severe PTSD resistant to conventional therapy received slow-release prazosin (half-life of 10.8 hours) added to their prescription for at least three months. PTSD symptoms were evaluated by the PCL-C, together with nightmares and insomnia items of CAPS, at baseline and at the last observation of each patient. **Results:** Two patients showed improvement in general symptoms of PTSD (reduction of 35.7% and 11.9% in PCL-C scores), and three showed relief from nightmares and insomnia (CAPS scores). The only patient who received morning and bedtime doses of prazosin showed the greatest improvement in general symptoms of PTSD. **Discussion:** It is possible that the sustained blockade of noradrenergic activity in the central nervous system provided by slow-release prazosin during the day is necessary to further ameliorate residual PTSD symptoms in patients receiving conventional antidepressant therapy.

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Keywords: Posttraumatic stress disorder, prazosin, pharmacotherapy, PTSD, alpha-1 adrenergic antagonist.

Resumo

Contexto: Prazosina, um antagonista de receptores alfa-1 adrenérgicos, é utilizada no tratamento de pesadelos e insônia relacionados com TEPT. Apesar das evidências sugerindo sua eficácia também no tratamento de sintomas gerais de TEPT, sua curta meia-vida (2-3 horas) pode limitar seus efeitos terapêuticos. **Objetivo:** Descrever quatro casos de pacientes com TEPT resistentes aos inibidores de recaptação de serotonina ou de serotonina e adrenalina (terapia convencional) tratados com uma apresentação de prazosina de liberação lenta. **Métodos:** Quatro pacientes com TEPT grave, resistentes à terapia convencional, tiveram a prazosina de liberação lenta (meia-vida de 10,8 horas) adicionada a suas prescrições por pelo menos três meses. Os sintomas de TEPT foram avaliados pela PCL-C e pelos itens referentes a pesadelos e insônia da CAPS, na linha de base e no final do período de observação de cada paciente. **Resultados:** Dois pacientes mostraram melhora dos sintomas gerais de TEPT (redução de 35,7% e 11,9% nos escores da PCL-C), e três mostraram melhora de pesadelos e insônia (nos escores da CAPS). O único paciente que recebeu doses da prazosina pela manhã e ao deitar-se foi o que mostrou a maior melhora dos sintomas gerais de TEPT. **Conclusão:** Possivelmente, a sustentação do bloqueio da atividade noradrenérgica no sistema nervoso central promovida pela prazosina de liberação lenta durante o dia se faz necessária para a melhora de sintomas residuais de TEPT em pacientes em tratamento convencional com antidepressivos.

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Palavras-chave: Transtorno do estresse pós-traumático, prazosina, farmacoterapia, TEPT, antagonista alfa-1 adrenérgico.

Introduction

Prazosin, a selective antagonist of alpha-1 adrenergic¹, shows evidence of being effective as adjunctive therapy in the treatment of posttraumatic stress disorder (PTSD)². Although some authors advocate that cognitive-behavioral therapy is the treatment of choice for PTSD³, the pharmacotherapy also has an important role in its treatment. For instance, the decreased quality of life associated with PTSD⁴, can be reversed with successful pharmacological treatment⁵. In spite of the selective serotonin reuptake inhibitors (SSRIs) being considered the first-line pharmacological treatment for PTSD⁶, these drugs show limited efficacy⁷. Different from the SSRIs, prazosin acts primarily in the noradrenergic system. Noradrenergic stimulation of limbic structures, as hippocampus and amygdale, by the *locus coeruleus* maintains alertness, attention and consolidates frightening experiences memories, necessary for the PTSD development⁸⁻¹².

The three published randomized controlled trials (RCTs) using prazosin as adjunctive therapy showed improvement in general PTSD

symptoms, particularly nightmares^{13,14} and insomnia². Similar results were reported by a handful of open trials¹⁵⁻²¹.

Prazosin's short half-life (2 to 3 hours) may limit its therapeutic effects during the day. In Brazil there is a slow-release presentation of prazosin available, which has a half-life of approximately 10.8 hours. This feature could be useful for treatment of PTSD daytime symptoms, especially those related to hyperexcitability^{20,22}, as well as nightmares and insomnia by night. Through case reports, the current paper describes, by the first time, the use of slow-release prazosin as adjunctive therapy in the treatment of refractory PTSD patients victims of urban violence.

Methods

Patients were selected from an outpatient clinic at *Universidade Federal do Rio de Janeiro*, specialized in posttraumatic stress assessment and pharmacological treatment. The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders – IV Axis

I Disorders (SCID)²³ was administered to the patients by a psychiatry with experience in clinical research (MV).

PTSD patients signed informed consent and received medical care on a monthly basis. At every consultation they have their PTSD symptoms severity evaluated by the Portuguese version²⁴ of *PTSD Checklist Civilian Version - PCL-C*²⁵. The PCL-C is a 17-item self-report questionnaire based on DSM-IV criteria for PTSD. Patients indicated to what degree they have been disturbed by PTSD symptoms during the last month, classifying them on a 5-point scale (1 = not at all to 5 = very much). The PCL-C score ranges from 5 to 85, with higher values implying more severe PTSD symptoms. According to the DSM-IV, PTSD symptoms can be grouped into three clusters: intrusive thoughts/re-experiencing (B criteria), avoidance/emotional numbing (C criteria), and hyperarousal (D criteria). To be considered as a probable PTSD case according to the PCL-C, patients should have a score greater than or equal to three in at least one item from group B (questions 1 to 5), three from C (questions 6 to 12) and two from D (questions 13 to 17). The Brazilian version of PCL-C has good internal consistency (Cronbach's $\alpha = .89$) and test-retest reliability ($r = .83$)²⁶.

All patients were treated with a SSRI or a selective serotonin/noradrenaline reuptake inhibitors (SNRIs) with the maximum tolerated/recommended dose for at least eight months. After that period, those patients who were still fulfilling the criteria for a probable PTSD case (PCL-C) and were presenting nightmares and insomnia, had their prescriptions augmented with prazosin. The patients who were still symptomatic, but did not have nightmares and insomnia as major complains were treated with other medications, which have greater scientific evidence for treatment of diurnal PTSD symptoms, such as risperidone or valproic acid⁷ and therefore were not included in this report.

The four patients selected to receive prazosin were additionally evaluated by the items addressing nightmares and insomnia (B2 and D1) of the Clinician Administered PTSD Scale (CAPS)²⁷ at baseline (before starting prazosin) and monthly thereafter. The CAPS is a structured interview which measures frequency (range, 0-4) and intensity (range, 0-4) of each PTSD symptom.

All these four patients received slow-release prazosin as add-on therapy. The slow-release presentation of prazosin has a half-life of 10.8h, four times longer than the conventional presentation, and reaches peak plasma concentration in about 3 hours. This presentation offers longer therapeutic effects and lower incidence of side effects²⁸. Prazosin was started at 1 mg/day, 1 hour before bedtime. Dosage was increased by 1 mg per visit according to efficacy and

tolerability. Due to its hypotensive effects all patients had their blood pressure monthly measured.

Results

As expected, at baseline all four patients met the DSM-IV criteria for PTSD, assessed by the PCL-C. They also scored a minimum of 4 points in at least one of the items of the CAPS investigated.

Tables 1 and 2 depict the period of time that each patient took prazosin, the maximum dose achieved, and their scores on PCL-C and CAPS at baseline and at their last observation, respectively. During this period, no patient showed clinical significant hypotension.

The following case reports describe four patients suffering from PTSD due to urban violence, who have received prazosin as add-on therapy.

Case 1

A 45-year-old white male truck driver had suffered a handful of assaults with fire guns while working. In the most striking one, his partner was murdered by his side inside the company truck. Since then, he began experiencing intrusive thoughts, flashbacks, recurrent nightmares related to trauma and, insomnia, in addition to persecutory ideas and of reference, among other symptoms. There was no history of mental disorders before trauma. However, after that he developed severe major depressive disorder with psychotic symptoms, OCD and, social phobia. Before starting prazosin, patient had received paroxetine (70 mg/day) and clonazepam (2 mg/day) for months, but nightmares and insomnia persisted. Therefore, prazosin was prescribed and increased up to 5 mg/day for 8 months, leading to a great improvement of nightmares and insomnia as measured by CAPS (Table 2) and of general PTSD symptoms according to PCL-C (Table 1). During this period, clonazepam dose could be reduced from 2 to 1 mg at night.

Case 2

A 45-year-old white female nursing assistant witnessed the hospital being shot by gunfire from a nearby slum. Since then, she started feeling extremely frightened when outside her house, startled to sounds similar to gun shots, had insomnia and recurrent nightmares that used to wake her up, among other symptoms. Before the trauma she already had obsessive-compulsive disorder (OCD) and somatoform

Table 1. PCL-C scores in PTSD treatment with prazosin

Case	Prazosin use		PCL-C															
	Time (months)	Maximum dose (mg/day)	Baseline								Last observation							
			Number of symptoms ≥ 3				Score				Number of symptoms ≥ 3				Score			
			B	C	D	Total	B	C	D	Total	B	C	D	Total	B	C	D	Total
1	08	5	5	4	5	14	19	17	22	58	2	3	4	09	13	18	14	45
2	03	3	5	5	5	15	23	28	24	75	5	6	5	16	24	28	23	75
3	06	10	5	6	5	16	20	25	18	63	5	5	5	13	21	28	20	69
4	24	8	1	4	2	07	11	19	12	42	1	2	2	05	09	17	12	38

Table 2. CAPS scores in PTSD treatment with prazosin

Case	Prazosin use		CAPS			
	Time (months)	Maximum dose (mg/day)	Baseline		Last observation	
			Nightmares	Insomnia	Nightmares	Insomnia
1	08	5	6	5	3	2
2	03	3	7	7	5	4
3	06	10	7	6	6	7
4	24	8	6	2	0	2

disorder. After that, she developed severe major depressive disorder without psychotic symptoms, body-dimorphic disorder and eating disorder not specified. At baseline, she was using venlafaxine (375 mg/day), amitriptyline (25 mg/day) and clonazepam (3 mg/day). Prazosin was prescribed and increased until 3 mg/day, with a slight improvement in nightmares and insomnia according to the CAPS (Table 2), and no change in general symptoms by PCL-C (Table 1). It is noteworthy that throughout this period the dose of clonazepam could be reduced from 3 mg/day to 2 mg/day.

Case 3

A 42-year-old white male bus driver accidentally hit and killed a child during work. He did not realize what happened until a colleague called his attention. Since then, the patient became to present auditory hallucinations (dead child crying), insomnia, nightmares related to the accident, avoidance behavior (could not ride a bus or even think about it), among other symptoms. He didn't suffer from any previous mental disorder, but after the trauma he developed severe major depressive disorder with psychotic symptoms, OCD and panic disorder with agoraphobia. Nightmares and insomnia were still major complains, despite treatment with venlafaxine (300 mg/day), nortriptyline (200 mg/day), clonazepam (3 mg/day) and chlorpromazine (50 mg/day) for months. Therefore, prazosin was prescribed and increased up to 8 mg/day for 6 months. At the end of this period, there was no reduction in PCL-C score (Table 1) or in CAPS items (Table 2). However, chlorpromazine could be suspended without worsening of insomnia.

Case 4

A 49-year-old black male bank officer suffered two assaults with fire guns at work. In the last one, he had a gun pointed against his neck and threatened by burglars who claimed to know personal information about him and his family. Thereafter, he began to experience flashbacks, intrusive thoughts, avoidance behavior, emotional numbing, irritability, recurrent nightmares, insomnia and hypervigilance. Before the assaults, he already had dysthymic disorder and OCD. Panic disorder with agoraphobia and specific phobia (elevators) were developed after trauma. He had been treated with paroxetine (50 mg/day), bupropion (300 mg/day) and clonazepam (0.8 mg/day) for months. Although he had partial relief of PTSD symptoms, nightmares related to assaults were still present. Thus, prazosin was prescribed and increased to 8 mg/day for 24 months, without changes in SSRIs prescription. At the end of this period, he achieved considerable improvement in nightmares as measured by CAPS (Table 2) and in general PTSD symptoms by PCL-C (Table 1). It was also possible to reduce clonazepam dose from 0.8 to 0.6 mg/day.

Discussion

Among the four cases reported here, two showed improvements in PTSD general symptoms according to PCL-C, and three showed relief from nightmares and insomnia, according to CAPS scores.

The scores of PCL-C indicated a reduction of 35.7% and 11.9% from baseline to the last observation in cases 1 and 4, respectively (Table 1). It is noteworthy that the patient 1 was the only one who received a morning dose of prazosin, in addition to the bedtime dose. Accordingly, he was also the one with the best improvement in PTSD general symptoms. Although the cases reported here cannot provide definitive conclusions, it is possible that the blockade of noradrenergic activity in the central nervous system during the day is necessary to improve the global PTSD symptoms, even in resistant patients as reported here.

Until now there are only five studies^{2,19,20,22,29} reporting the use of daytime prazosin dose in patients with PTSD (two case reports, one chart review, one open-label study, and only one randomized clinical trial). However, most of these studies used an additional

dose of prazosin in the early afternoon, and none of them used a therapeutic scheme that warrants central noradrenergic blockade during almost 24h.

Compared to its conventional presentation, the use of slow release prazosin could be an advantage for the treatment hyperexcitability-related PTSD symptoms, which tend to show a better response when a daytime dose of prazosin is also administered²⁰. Moreover, this presentation of prazosin produces less adverse effects. Patient 1 showed severe daytime symptoms related to hyperexcitability, irritability, explosiveness, alertness and was easily startled. The prazosin administration at night resulted in a decrease of 3 points in each of the CAPS items (Table 2), but not in PCL-C scores (Table 1). Due to the maintenance of these symptoms for two months even after night administration of prazosin, an additional morning dose was added to prescription. At that time, PCL-C scores were almost unchanged compared to baseline (59 and 58 points, respectively). However, after introducing the diurnal dose of prazosin, there was a decrease of 14 points in PCL-C score of patient 1. It's noteworthy that comparing to other symptom clusters, hyperexcitability was the one that showed de greater reduction in PCL-C scores in this patient. In addition, comparing to the other patients, patient 1 also showed the greater decrease in PCL-C hyperexcitability cluster (Table 1). Considering that there were no changes in the prescription of antidepressants, this decrease in the PCL-C scores suggests that the addition of a diurnal dose of prazosin may be effective for the treatment of PTSD symptoms other than nightmares and insomnia.

It is noteworthy that the administration of prazosin allowed us to reduce or suspend drugs with sedative or hypnotic purposes (i.e. clonazepam and chlorpromazine) in four cases. It has particular importance in PTSD treatment, since patients with PTSD have high rates of substance abuse³⁰, especially benzodiazepines³¹.

Some limitations of the current report of cases in the small number of subjects; its naturalist feature, what allowed changes in the prescription of the other medications; and that, due practical reasons, the authors applied only the items regarding nightmares and insomnia of the CAPS, as opposed as the whole interview.

Conclusion

This is the first report of cases addressing the efficacy of prazosin in the treatment of PTSD in Brazilian patients. This fact gives an especial relevance for the current report, since ethnicity is an important, but often ignored factor in psychopharmacology³². Even though, our results are in accordance with those reported in North American studies. Although currently the efficacy of prazosin in the treatment of insomnia and nightmares in patients with PTSD is taken for granted, additional multicenter randomized clinical trials with a sound number of patients from diverse countries are necessary to evaluate the real efficacy of prazosin. Finally, it is possible that a 24h blockade of central noradrenergic activity in the nervous system provided by the administration of slow release prazosin twice a day can also ameliorate residuals symptoms of PTSD that could not be vanished by antidepressant treatment. However, this hypothesis needs to be further investigated by large RCTs.

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