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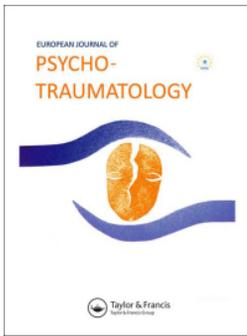
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A non-randomized pilot trial of the use of prazosin in the prevention of transition from acute stress disorder to post-traumatic stress disorder

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ABSTRACT

Background: Following a traumatic event, 40–80% of the patients with acute stress disorder (ASD) will develop post-traumatic stress disorder (PTSD), 67% at 6 months. Alpha1-blockers are effective in treating some symptoms of PTSD but their usefulness in acute stress situations remains unclear. We hypothesized that reducing noradrenergic hyperactivity with an alpha1-blocker during the acute phase after a traumatic event could prevent the transition to PTSD in patients with ASD.

Objective: To investigate the efficacy and safety of a 1-month course of alpha1-blocker (prazosin) to prevent the transition to PTSD in patients with ASD at 6 months.

Method: In a monocentric open-label prospective pilot study, 15 patients with ASD were included within 3–7 days of exposure to a traumatic event. After enrolment, they received prazosin LP at home at bedtime at 2.5 mg/day for 7 days and then 5 mg/day for 21 days. Incidence of PTSD was assessed at 6 months using the Clinician Administered PTSD Scale (CAPS).

Results: At 6 months, 22% of patients who completed the study (2/9) met the diagnostic criteria for PTSD. This rate was significantly lower than that observed in previous studies (67%; $p = .047$). The treatment was well tolerated and there were no serious adverse events.

Conclusions: These preliminary findings indicating the safety of prazosin and suggesting its potential to prevent the development of PTSD in ASD require to be replicated in large-scale randomized placebo-controlled studies.

Trial registration: The study was pre-registered on a public database (www.clinicaltrials.gov identifier: NCT03045016).

Un ensayo clínico piloto no aleatorizado del uso de prazosina en la prevención de la transición del trastorno de estrés agudo al trastorno de estrés postraumático

Antecedentes: Luego de un evento traumático, el 40–80% de los pacientes con trastorno de estrés agudo (TEA) desarrollará el trastorno de estrés postraumático (TEPT), el 67% lo hará a los 6 meses. Los bloqueadores alfa de tipo 1 son efectivos en tratar algunos síntomas del TEPT; sin embargo, su utilidad en las situaciones de estrés aguda no está clara. Tenemos la hipótesis que reducir la hiperactividad noradrenérgica con un bloqueador alfa 1 durante la fase aguda después de un evento traumático podría prevenir la transición a TEPT en pacientes con TEA.

Objetivo: Investigar la eficacia y seguridad de un curso de 1 mes con un bloqueador alfa 1 (prazosina) para prevenir la transición a TEPT en los pacientes con TEA a los 6 meses.

Métodos: Se realizó un estudio piloto prospectivo abierto monocéntrico, se incluyeron 15 pacientes con TEA dentro de los 3 a 7 días posterior a la exposición de un evento traumático. Después del registro, recibieron prazosina LP en casa, a dosis de 2.5 mg/day por 7 días antes de dormir; y después a dosis de 5 mg/day por 21 días. La incidencia del TEPT se evaluó a los 6 meses utilizando la Escala de TEPT administrada por el clínico (CAPS).

Resultados: A los 6 meses, el 22% de los pacientes que completaron el estudio (2/9) cumplieron los criterios diagnósticos para el TEPT. Esta tasa fue significativamente menor en comparación a las observadas en estudios previos (67%; $p = .047$). El tratamiento fue bien tolerado y no se reportaron eventos adversos severos.

Conclusiones: Estos hallazgos preliminares que indican la seguridad de la prazosina y sugieren

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Prazosina; prevención; estrés agudo; bloqueador alfa 1; TEPT

关键词

哌唑嗪; 预防; 急性应激; α 1-阻滞剂; PTSD

HIGHLIGHTS

- Alpha1-blockers are safe and well tolerated in patients with acute stress disorder.
- The use of alpha1-blockers 3–7 days after traumatic exposure is worthy of study.
- Alpha1-blockers could prevent the transition to PTSD in ASD patients at 6 months.

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su potencial para prevenir el desarrollo de TEPT en las personas con TEA, los resultados deben replicarse en estudios clínicos aleatorizados y controlados con placebo a gran escala.

Registro del ensayo: El estudio fue pre-registrado en una base de datos pública (www.clinicaltrials.gov identificador: NCT03045016).

使用哌唑嗪预防急性应激障碍向创伤后应激障碍转变的非随机试点试验

背景: 创伤事件后, 40–80% 的急性应激障碍 (ASD) 患者会发展为创伤后应激障碍 (PTSD), 6个月时为 67%。Alpha1 受体阻滞剂可有效治疗 PTSD 的某些症状, 但其在急性应激情况下的作用仍不清楚。我们假设在创伤事件后的急性期使用 α_1 受体阻滞剂减少去甲肾上腺素能亢进可以防止 ASD 患者向 PTSD 转变。

目的: 探究 1个月疗程的 α_1 受体阻滞剂 (哌唑嗪) 预防自闭症谱系障碍 (ASD) 患者在 6个月时转变为创伤后应激障碍 (PTSD) 的有效性和安全性。

方法: 在一项单中心开放标签前瞻性试点研究中, 纳入了遭受创伤事件后 3 至 7 天内的 15 名患有自闭症谱系障碍 (ASD) 患者。入组后, 他们在家中睡前接受哌唑嗪腰椎穿刺, 剂量为 2.5毫克/天, 持续 7 天, 然后为 5毫克/天, 持续 21 天。在 6个月时使用临床医生管理 PTSD 量表 (CAPS) 评估 PTSD 的发生率。

结果: 6个月时, 完成研究的患者中有 22% (2/9) 符合 PTSD 的诊断标准。这一比率明显低于之前研究中观察到的比率 (67%; $p = .047$)。治疗耐受性良好, 没有发生严重不良事件。

结论: 这些初步研究结果表明哌唑嗪的安全性, 并表明其预防 ASD 患者发展为 PTSD 的潜力, 需要在大规模随机安慰剂对照研究中得到重复。

1. Introduction

Acute stress disorder (ASD) is a short-term and common mental health condition that can occur between 3 days and one month after exposure to a stressful traumatic event. When symptoms last for more than a month, post-traumatic stress disorder (PTSD) may be diagnosed (American Psychiatric Association, 2013). Previous studies have reported that 40% to 80% of patients diagnosed with ASD will develop PTSD (Bryant, 2005; Bryant et al., 2015; Harvey & Bryant, 1998; Harvey & Bryant, 2000), 67% at 6 months (Harvey & Bryant, 1998). As chronic PTSD is a very difficult condition to treat, often leading to serious complications (Blanco et al., 2013; Cogle et al., 2009), preventing the transition to PTSD in patients with ASD is a major challenge, but no preventive approach is available (VA/DoD Clinical Practice Guidelines 2018).

At a biological level, it has been proposed that, in the event of intense stress, the binding of norepinephrine to α_1 receptors may lead to dissociative symptoms by inhibiting prefrontal cortex while increased activity in the amygdala would increase the memorization of the stressful event, leading to symptoms of hypervigilance, flashbacks and traumatic nightmares (Arnsten et al., 2015). Prazosin, an α_1 -adrenoceptor antagonist (α_1 -blocker) commonly used to treat hypertension, has been shown to be effective in reducing some traumatic symptoms in patients with PTSD (Reist et al., 2021), particularly nightmares. We hypothesized that reducing stress-induced activation of the noradrenergic system by blocking α_1 -receptors could lead to a reduction in traumatic symptoms and prevent the development of PTSD in patients with ASD. The aim of this pilot study was to test whether a one-month course of

prazosin would be effective and safe in preventing the development of PTSD in patients with ASD six months after exposure to the traumatic event. We also hypothesized that, compared with the 67% transition rate observed in previous studies (Harvey & Bryant, 1998), the incidence of PTSD at 6 months would be significantly lower in patients who received prazosin.

2. Method

In an open-label prospective non-randomized pilot study, patients who met DSM-5 criteria for ASD received prazosin LP at home at bedtime for 28 days (2.5 mg/day for 7 days, then 5 mg/day for 21 days). Our primary outcome was the number of patients meeting criteria for PTSD at 6 months, as assessed by the Clinician-Administered PTSD Scale (CAPS) (Blake et al., 1995). The severity of depressive symptoms severity was assessed at month 6 using the 13-item Beck Depression Inventory (BDI_{13}). The Peritraumatic Distress Index score (PDI) and Peritraumatic Dissociation score (PDEQ) were assessed at baseline. Regarding safety, all adverse events, particularly those known to be associated with prazosin, such as orthostatic hypotension, were carefully recorded throughout the study.

We calculated that 10.4 participants would be sufficient to detect a transition to PTSD with an incidence of 25% with 95% confidence (Viechtbauer et al., 2015). With an attrition rate similar to that observed in a previous study (44%) (Harvey & Bryant, 1998), we estimated that a pilot study of 15 participants would be necessary to reach our goal. We, therefore, decided to screen at least 24 patients for inclusion in the trial.

2.1. Population

The target population consisted of adults with ASD admitted to the psychiatric emergency unit or the legal/forensic medicine services of the Edouard Herriot Hospital in Lyon. They had to have experienced a traumatic event as defined by the DSM-5 (death, threat of death, actual or threatened serious injury) within 3–7 days prior to enrolment.

Non-inclusion criteria were: contraindication to prazosin, alcohol or drugs use at the time of the event, history of psychosis and PTSD, suicide risk, persistence of a life-threatening injury, severe head trauma (Ruff et al., 2009), prescription of morphine, pregnancy or breastfeeding, absence of effective contraception in a woman likely to reproduce. Only direct exposure was selected and sexual assault was excluded to homogenize the population (Harvey & Bryant, 1998; Harvey & Bryant, 2000; Nöthling et al., 2022).

2.2. Ethic and regulatory considerations

The study was approved by an ethics committee (CPP West 6) on 13 December 2016 (no. 69HCL16-0628) and pre-registered on a public database (Identifier ClinicalTrials.gov: NCT03045016). All the patients signed a written informed consent after a detailed description of the study.

3. Results

3.1. Population characteristics

Between April 2017 and September 2020, 30 patients were screened for eligibility, of whom 15 were included. Most were recruited from the emergency department of a general university hospital. The screened patients who were not included either refused to participate or met at least one non-inclusion criterion (Figure 1). Of the included patients who had been physically assaulted (73%), 4 had been assaulted by someone close to them and 7 by a stranger (assault on the road, violent burglary, assault at work). None of the patients suffered serious somatic trauma, but two required specific treatment (orbital floor fracture and stab wound to the shoulder). Two patients had a psychiatric history (depressive episode and suicidal crisis) and two others had a traumatic history (assault at work). At inclusion, the mean PDI score was $33.7 \pm$ standard deviation 7.3, the mean PDEQ score was 32.7 ± 8.5 , and patients met 10.5 ± 1.2 DSM 5 diagnostic criteria for ASD.

3.2. Effectiveness

Of the 15 patients included, 9 completed the 6-month visit, corresponding to an attrition rate of 40% (Figure 1). Of the 9 patients who completed

the study, only 2 met the diagnostic criteria for PTSD as assessed by the CAPS (22%) at month 6 (patients #7 and #9; Table 1); patient #7 had a total CAPS score of 54 and patient #9 had a score of 42 (17.0 ± 18.6 in the whole sample). There was no evidence of moderate or severe depressive symptoms on the BDI₁₃ at month 6 (7.1 ± 5.3 in the whole sample).

We used Fisher's exact test to exploratory compare our results with those from three previous studies that included a comparable population (Harvey & Bryant, 1998; Harvey & Bryant, 2000). In the first study (Harvey & Bryant, 1998), of the 43 patients with ASD included, 24 completed the 6-month assessment period, of whom 16 met the criteria for PTSD (67%). In the current study, the transition rate at 6 months was significantly lower (2/9 versus 16/24, $p = .047$).

In the second study (Harvey & Bryant, 2000), the same group of authors reported that of the 10 patients who completed the assessment at 2 years, 8 were diagnosed with PTSD (80%) (Harvey & Bryant, 2000). There was also a significant difference in the number of patients who developed PTSD at follow-up ($p = .02$).

3.3. Safety

The treatment was well tolerated. There were no serious adverse events throughout the study. All tests for orthostatic hypotension tests were negative. A few transient and harmless side effects were observed, which disappeared after discontinuation of treatment: dizziness, fatigue, tinnitus, headache, and nausea. No patient discontinued treatment due to an adverse event.

4. Discussion

In this prospective, open-label pilot study, fifteen patients received prazosin LP for one month after exposure to a traumatic event. The aim of the present study was to determine whether there was sufficient evidence to conduct a randomized, placebo-controlled trial on the beneficial effect of prazosin in preventing PTSD in patients with ASD. Among patients who completed the trial, the transition rate observed of 22% (2 out of 9) was in line with the anticipated 25% and was lower than the rates found in previous comparable trials: 67% at 6 months (Harvey & Bryant, 1998) and 80% at 2 years (Harvey & Bryant, 2000). In the worst-case scenario, a scenario where all the patients who dropped out developed PTSD, the current study would have revealed a transition rate of 53% (8/15), a rate comparable to that observed in previous studies; in the best-case scenario, if all patients who dropped out did not develop PTSD at 6 months, a transition rate of 13% (2/15) would have been observed.

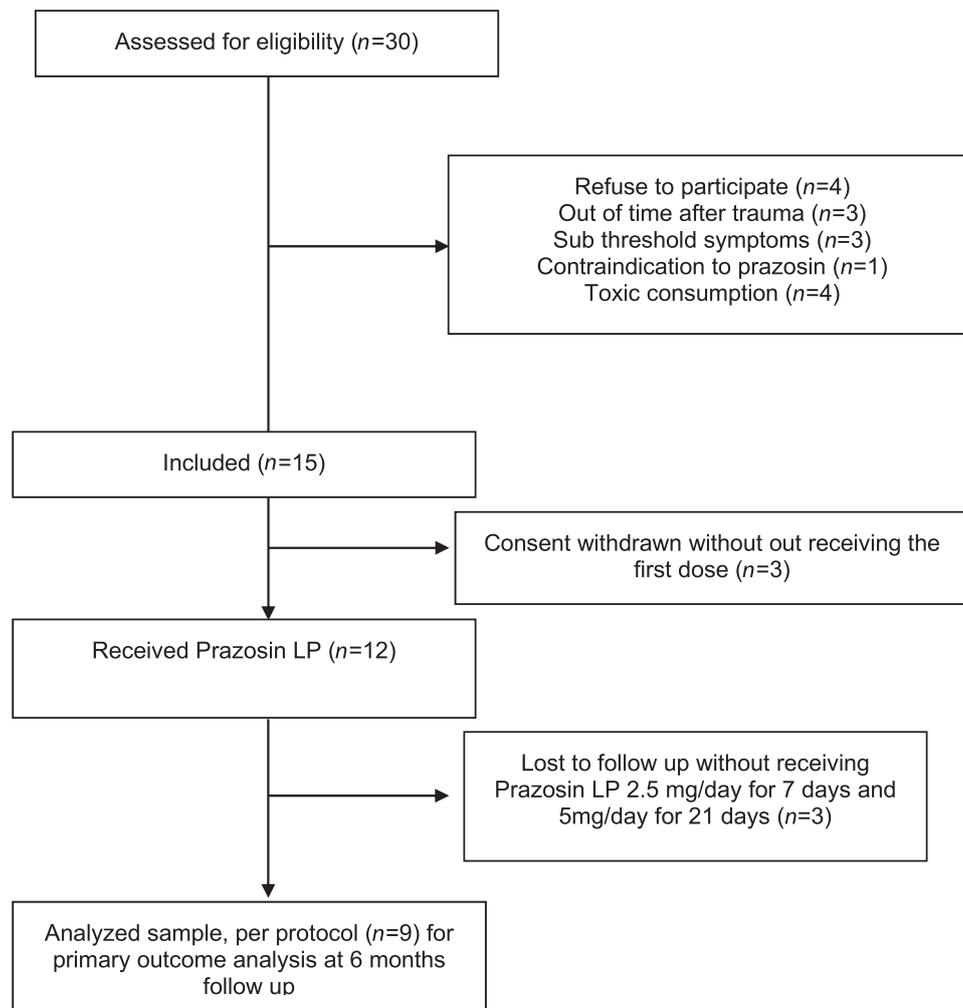


Figure 1. CONSORT Flow diagram of the PRAZOSTRESS study. Flow chart showing the screening, the inclusion and the number of patients who completed the study.

At month 6, six patients dropped out of the study. Despite the procedures in place to contact participants who dropped out (phone calls, emails, etc.),

no data were available to monitor patient progress. The attrition rate observed (40%) was similar to that observed in previous comparable studies (44.2%)

Table 1. Clinical and demographic characteristics of included patients with ASD.

	Baseline characteristics							Characteristics at month 6		
	Age (y)	Sex	Type of trauma	Medication	PDI	PDEQ	ASD (n)	CAPS	BDI ₁₃	PTSD diag
1	18	M	Road accident	None	24	28	9	–	–	NA
2	23	M	Physical assault	Paracetamol 4 g/day	40	26	10	–	–	NA
3	23	F	Physical assault	None	44	33	13	19	4	No
4	36	F	Physical assault	None	34	30	10	12	12	No
5	26	F	Physical assault	Diazepam 10 mg/day	26	43	11	–	–	NA
6	36	M	Physical assault	HIV triple therapy Salbutamol Tramadol 100 mg/day	36	33	11	–	–	NA
7	36	F	Domestic arson	Sodium alginate	37	30	10	54	14	Yes
8	46	F	Physical assault	Paracetamol 4 g/day	38	43	9	–	–	NA
9	37	F	Physical assault	None	34	36	11	42	14	Yes
10	26	M	Physical assault	None	32	25	10	4	ND	No
11	37	M	Physical assault	Paracetamol 4 g/day	29	17	9	4	2	No
12	20	F	Physical assault	None	49	50	12	–	–	NA
13	19	M	Road accident	None	29	39	12	0	3	No
14	22	M	Road accident	None	22	25	10	10	3	No
15	48	M	Physical assault	Hydoxyzine 25 mg/day Ketoprofen	32	33	11	8	5	No
Mean (SD)	30.2 (9.8)	8M/ 7F			33.7 (7.3)	32.7 (8.5)	10.5 (1.2)	17.0 (18.6)	7.1 (5.3)	2 Yes

Note. M: male; F: female; PDI: peritraumatic distress score; PDEQ: peritraumatic dissociation score; y: years; BDI₁₃: Beck Depression Inventory score; CAPS: Clinician Adminstrated PTSD Scale total score; ASD (n): number of DSM 5 criteria of ASD at baseline; PTSD diag: diagnosis of PTSD according to DSM 5 criteria at month 6. The 2 participants who developed PTSD are shown in bold (patients #7 & #9).

(Harvey & Bryant, 1998) and was in line with the attrition rate estimated in the calculation of the sample size for this pilot study.

No serious adverse events occurred and the treatment was well tolerated by participants, including known adverse effects of prazosin such as orthostatic hypotension.

The interpretation of these results is limited by the pilot nature of the study and the lack of a placebo-controlled group. The generalizability of the results of the present study is also limited by the fact that only one measurement point was used at 6 months. Future randomized trials should consider assessing patients at 3 months and 1 year. Furthermore, as sexual assault victims are more likely to have a history of previous trauma, which increases the risk of complex PTSD (Nöthling et al., 2022), we decided to exclude them from this pilot study. The present results should therefore be essentially valid for physical assault and road traffic accidents, and require further replication in this specific population. Participants were not offered psychotherapy during the study period, as this would have altered symptomatology. This could be ethically questionable, as standardized psychotherapies such as cognitive behavioral therapy and eye movement desensitization and reprocessing (EMDR) are strategies with a high level of evidence for ASD. However, in clinical practice, these therapies are rarely used within the first six months, mainly due to a lack of available therapists. At the end of the study period, the two participants with persistent PTSD were given contact details of therapists for optimal management.

Although there is a controversy about the efficacy of prazosin for global PTSD symptoms in patients with chronic PTSD (Reist et al., 2021), such as veterans (Raskind et al., 2018), its value in preventing the transition to full-blown PTSD in the early phase after trauma exposure, such as in patients with ASD from the general population, needs to be studied in depth, as the current findings suggest.

Disclosure statement

No potential conflict of interest was reported by the author(s).

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Authors' contributions

E.P. & C.M. designed the study, C.M., E.P. & L.F. included participants, J.B & C.M. drafted the first version of the manuscript; Ph.V. & L.F. helped in the interpretation of the data.

Data availability statement

The raw data are provided in Table 1, other data are available on reasonable request.

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