Refractory nightmares in post-traumatic stress disorder: remission with prazosin

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Dear Editor,

Post-traumatic stress disorder (PTSD) is an anxiety disorder whose prevalence in different populations depends on exposure to triggering traumatic factors[1], in the genesis of which noradrenergic[2] dysregulation has been postulated. It includes four types of symptoms: re-experiencing the traumatic event, avoidance, hyperexcitation, and negative thoughts and moods or feelings. Repetitive nightmares of the event are included in the first group. The effectiveness of treatments for PTSD has been thoroughly studied, nonetheless, the effectiveness of specific treatments for nightmares is less well known[3]. Prazosin is an alpha-adrenergic antagonist initially used for PTSD in case series observed by Dr. M. Raskind, who observed an improvement in nightmares when prazosin was administered for other reasons. He and his group postulated that, by crossing the blood-brain barrier, prazosin could be effective in hyperexcitation symptoms, despite being a non-sedating drug[4].

We present the case of a 36-year-old woman, with no medical or surgical history of interest, who develops symptoms of serious PTSD after suffering an attempted hit-and-run by a neighbour with whom she had problems. Despite emerging physically unharmed from the attempted assault, approximately two weeks after the event she developed clinical symptoms compatible with the diagnosis of post-traumatic stress disorder (daily flashbacks , avoidance behaviour to the extreme of home seclusion, free-floating anxiety and hyperalert state). Treatment with sertraline began with progressively increasing doses up to 200mg/day, clonazepam up to 4 mg/day and trazodone up to 200 mg per night, alongside cognitive-behavioral psychotherapy with the resident clinical psychologist during the whole process. Despite acceptable control of diurnal symptoms, nightmares remained virtually unchanged, causing frequent startled nocturnal awakenings, sweating, tachycardia and a choking sensation. Treatment with nocturnal quetiapine was attempted, but had to be stopped due to low tolerance.

After a bibliographic review of the case, the decision was made to try prazosin as a treatment for nightmares, reaching 10mg dose in a progressively increased pattern over a six week period. The aforementioned treatment was maintained with the exception of quetiapine. The benefits began to be evident in the third week, but it was not until the 10 mg dose was reached that the nightmares completely subsided. The patient's baseline blood pressure (BP) figures were around 135/80. When the fully effective dose for the remission of nightmares was reached, average daytime figures (self-measurement of BP with a digital arm tensiometer) fell to 120/70-75, with no symptoms of dizziness, syncopes or any other noticeable adverse effect. At present, 10 months after starting treatment, the same doses of prazosin are maintained, trazodone has been completely discontinued and clonazepam has been reduced to 1-1.5 mg/day. No indication has been found in the bibliographic review regarding when it would be convenient to withdraw the treatment.

Prazosin is indicated in the treatment of arterial hypertension, Raynaud's phenomenon and benign prostatic hypertrophy. Four studies by the Raskind group between 2003 and 2013 offer very positive results in the treatment of nightmares. The impact on PTSD symptoms was two times better with drug than with placebos, which can translate into an effect size of 1.0. If only the effect on nightmares is measured, a 200% increase over placebos was found, translating into an effect size of 2.0, versus only 0.23 presented by selective serotonin reuptake inhibitors in PTSD symptoms (meaning they are 23% better than placebos), according to 2015 meta-analysis[1].

One of the limitations postulated in its use for the treatment of nightmares in PTSD is the time it takes to titrate the dose necessary for improvement. Thus, two studies show that 85% to 90% of patients with prazosin receive a subtherapeutic dose and prescribers give up prematurely. Two different titration protocols have been proposed according to sex (male/female)[5-6]:

Men: start with 1 mg at night for two nights, 2 mg for 5 nights, then 4 mg for 7 nights. Then and in weekly dose increments: 6 mg, 10 mg and 15 mg. The average dose was 15.6 mg and the maximum dose 25 mg (taken at night). It took a total of 5 weeks to reach the average dose. In order to boost improvement in daytime symptoms and due to the short half-life of the drug, Raskind incorporated a 1 mg mid-morning dose (about 10-11am) in the second week, for one week, then 2 mg for the following two weeks and finally 5 mg in the fifth and sixth weeks.

Women: 1 mg nightly for 3 nights, 2 mg for 11 nights, 4 mg 7 nights, 6 mg 7 nights up to a maximum dose of 10 mg on day 29. Similarly, a 1 mg mid-morning dose starting

in the second or third week and 2 mg starting in the fifth or sixth week. The average dose was 7 mg.

Similarly, prazosin has been shown to be effective and generally well tolerated in the same indication in children and adolescents[7]. Higher blood pressure levels prior to prazosin treatment have been shown to predict better outcomes in the treatment of nightmares[8]. More recently, several studies have shown that doxazosin, another alpha-1 adrenergic antagonist with a longer half-life than prazosin, although with less passage through the blood-brain barrier, is also effective in treating nightmares associated with PTSD[9,10]. Some authors postulate that it could be more effective in diurnal symptoms due to this higher half-life[10], although in this case prazosin was chosen due to the greater number of positive studies to date and the fact that the control of diurnal symptoms was already acceptable with prescribed treatment.

In conclusion, the present clinical case shows the efficacy of prazosin in the treatment of nightmares associated with PTSD. We should consider incorporating this drug into our therapeutic arsenal.

CONFLICT OF INTERESTS

None to disclose.

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Clozapine-induced eosinophilia, elevated C-reactive protein and fever

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Dear Editor,

Clozapine is an atypical antipsychotic, which may be useful in resistant psychosis[1]. However, its benefit are limited by hematological side effects such as eosinophilia, which can occur in a highly variable manner with a cumulative incidence of 5.9% after one year of treatment in responders[2].

Chatterton described a series of cases of eosinophilia induced by clozapine, which had a good prognosis, thus enabling the antipsychotic treatment to be maintained[3]; however, other case reports have described cases of organ dysfunction requiring immediate interruption of the treatment[4-6]. The decision to withdraw clozapine should be based on close observation and serial blood analyses.

Case reports facilitate the accumulation of knowledge about the possible clinical presentations and severity of clozapine-induced eosinophilia so that clinical decisions can be made based on case evidence that has been analyzed and presented in articles published by scientific journals.

Clinical case

the patient is a 17-year-old woman with a history of moderate intellectual disability (Wechsler Intelligence Scale for Children at age 12, intelligence quotient: 50, indicating a need for care in all vital activities, and psychic functional diversity of 56%). The patient went to Neuropediatrics from the age of 12 due to aggressiveness and periods of asthenia. Blood tests, brain images, electroencephalogram, and cytogenetic study were all normal; however, as the patient's behavior did not improve with antipsychotics, she was referred to Mental Health Services.

At age 16, the patient presented with an insidious onset of episodes of psychomotor exaltation, irritability, behavioral disinhibition, loss of interpersonal distance and both verbal and physical aggression. The patient also experimented megalomaniac and persecutory delusional ideas, with soliloquies and hallucinatory phenomena, lasting for two weeks. She was admitted to the Adolescent Psychiatry Unit, where she was diagnosed with Bipolar Disorder in a Manic Phase with Psychotic Symptoms. Initial treatment was lithium salts together with aripiprazole; however, at a second admission, it was necessary to add sodium valproate.

At her last visit to the Psychiatric Emergency Department, the patient's parents described a new manic decompensation, despite therapeutic compliance, due to the poorly tolerated and insufficient effect of the antipsychotics and the partial effectiveness of two mood stabilizers, with blood levels in the therapeutic range. Clozapine 25 mg/day was started, increasing to a maximum of 150 mg/day because higher doses cause sedation; aripiprazole dose was withdrawn in parallel with increase in clozapine dose. An important decrease of the manifest psychotic symptoms was achieved, and the initial blood tests showed no abnormalities; the eosinophils were at 240 cells/uL (normal up to 500 cells/uL).

On the 13th day of treatment, a fever peak of 39.1ºC was reported with malaise, sinus tachycardia, arthralgias, myalgia, and a headache. The physical examination was anodyne, and the blood tests showed leukocytosis with neutrophilia; the eosinophils were 220 cells/UL and C-reactive protein (CRP) had increased to 80 mg/L (normal range is 0-5 mg/L). The case was handled by Internal Medicine, who initially considered a viral process, for which oral paracetamol was administered, achieving provisional improvement in general malaise and fever, as shown in curve B of Figure 1.

No changes were evident for several days, and the electrocardiogram, chest x-ray, abdominal ultrasound, blood and urine cultures, viral polymerase chain reaction, serology, cardiac enzymes, and immunity test were normal. Serial blood counts showed no change until day 21, when eosinophils rebounded to 480 cells/UL with a normal number of leukocytes, and the CRP rose to 163 mg/L; leading to a worsening of general malaise and a new febrile peak. Internal Medicine initiated empirical antibiotic therapy with amoxicillin/clavulanic acid, without changes to the patient's symptoms.

On the 25th day, the patient's symptoms worsened worsened; the eosinophils rose to 530 cells/UL with a CRP remaining around 80 mg/L (Fig. 1). Internal Medicine changed the antibiotic to piperacillin/tazobactam without response. Owing the lack of progress with broad-spectrum antibiotic therapy, the inflammatory reaction to clozapine was considered as a possibly cause and it was thus discontinued despite the patient's psychopathological stability.

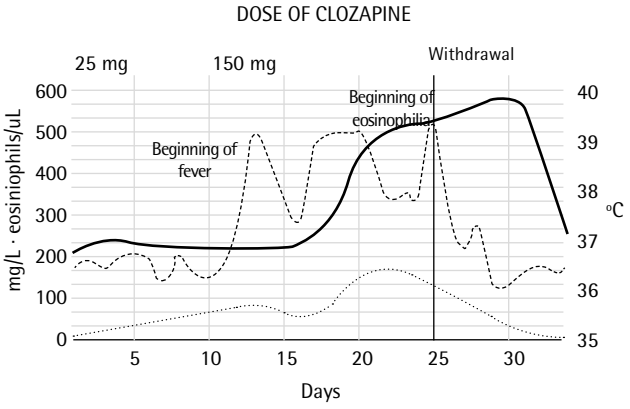

Figure 1 — *Graph of evolution. (-) Eosinophils count (per uL); (--) Maximum temperature of the day (ºC); (...) CRP (mg/L). The withdrawal of clozapine on the 25th day and subsequent improvement in the parameters are indicated.*

Twenty four hours after the withdrawal, the patient's fever disappeared definitively and the patient gradually recovered completely on a physical level. Blood tests showed that the eosinophils had returned to normal range. Without an antipsychotic, the hyperthymic symptoms recurred until the patient present again with a Manic Episode with Psychotic Symptoms; thus, it was necessary to include the patient in the electroconvulsive therapy program.

Discussion

clozapine is an antipsychotic that can cause various side effects in frequency and severity. The "very frequent" (≥1/10) side effects mentioned in the data sheet include drowsiness, tachycardia, constipation, and sialorrhea; and the "frequent" reactions (≥1/100, <1/10), include fever and eosinophilia[7]. The latter are mentioned as reactions that may be benign but that require follow-up. An association between fever, eosinophilia, elevated CRP, and flu-like symptoms is not specified.

In the case described above, the patient's nonspecific symptoms began 13 days after the start of treatment (five days after a stable dose of 150 mg); blood tests showed neutrophilia and normal numbers of eosinophils. Therefore, the initial management focused on an infectious picture, but the clinical worsening, normalization of neutrophilia, increase in the number of eosinophils, and the lack of response to broad-spectrum antibiotic therapy; contradicted this hypothesis.

An adverse reaction to clozapine was proposed as an alternative cause, but in the absence of prognostic certainty, a study was made of the possible scenarios to reach a decision. The majority of bibliographical references are reports of cases with a wide range of severity from benign symptoms[3,8] (isolated eosinophilia or fever that allows the continuation of treatment) to severe systemic inflammatory reactions[9-11] (which could require interruption). We found no published cases of increased inflammatory markers, flu-like symptoms, and subsequent eosinophilia, as observed in this case.

Among the severe reactions, eosinophilic myocardiopathy was ruled out in this patient due to the absence of markers of myocardial suffering. However, a prospective study reported that the increase in CRP may be an early indicator of developing myocarditis[12].

We selected two of the statistical tools most commonly used to calculate the association of this reaction with clozapine: the Naranjo algorithm[13] (Table 1) and the World

Table 1 **Naranjo Algorithm[13]. Definite≥9; probable 5-8; possible 1-4; doubtful≤0. Score: 5 (probable association).**

		Yes	No	Do not know	Score
1.	Are there previous conclusive reports on this reaction?	+1	**0**	0	**0**
2.	Did the adverse event appear after the suspected drug was administered?	**+2**	-1	0	**+2**
3.	Did the adverse reaction reappear when the drug was readministered?	**+1**	0	0	**+1**
4.	Are there alternative causes (other than the drug) that could on their own have caused the reaction?	+2	-1	**0**	**0**
5.	Did the reaction reappear when a placebo was given?	-1	**+2**	0	**+2**
6.	Was the drug detected in the blood (or other fluids) in concentrations known to be toxic?	-1	+1	**0**	**0**
7.	Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	**0**	**0**
8.	Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	**0**	**0**
9.	Was the adverse event confirmed by any objective evidence?	+1	**0**	0	**0**
10.	Was the adverse event confirmed by any objective evidence?	+1	**0**	0	**0**
Total					**5**

Table 2	World Health Organization Uppsala Monitoring Center Criteria (WHO-UMC)[14]
Certain	• Event or laboratory test abnormality, with plausible time relationship to drug intake. • Cannot be explained by disease or other drugs • Response to withdrawal plausible (pharmacologically, pathologically). • Event definitive pharmacologically or phenomenologically (i.e. an objective and specific medical disorder or a recognised pharmacological phenomenon). • Rechallenge satisfactory, if necessary.
Probable / Likely	• **Event or laboratory test abnormality, with reasonable time relationship to drug intake.** • **Unlikely to be attributed to disease or other drugs.** • **Response to withdrawal clinically reasonable.** • **Rechallenge not required.**
Possible	• Event or laboratory test abnormality, with reasonable time relationship to drug intake. • Could also be explained by disease or other drugs. • Information on drug withdrawal may be lacking or unclear.
Unlikely	• Event or laboratory test abnormality, with a time to drug intake that makes a relationship improbable (but not impossible). • Disease or other drugs provide plausible explanations.
Conditional / unclassified	• Event or laboratory test abnormality. • More data for proper assessment needed, or • Additional data under examination.
Unassessable / unclassifiable	• Report suggesting an adverse reaction. • Cannot be judged because information is insufficient or contradictory. • Data cannot be supplemented or verified.

Health Organization Uppsala Monitoring Center criteria (WHO-UMC)[14], (Table 2). In both cases, a "probable association" was achieved.

Given the clinical pattern of probable intolerance to clozapine, with a possible evolution towards systemic severity, the decision was made to withdraw the antipsychotic. The clinical and hematological normalization practically immediate to treatment, pointed to causal relationship.

Conclusions and recommendations

for clozapine, the epidemiological estimates of some of its side effects are known, and the decision to continue or discontinue its use may thus be based on known clinical evolutions of such circumstances. However, the idiosyncratic reactions, make it difficult to diagnose these reactions and decide about the maintenance or withdrawal of the drug.

This case presentation finds a "probable association" in the pharmacovigilance scales between clozapine and eosinophilia, fever, flu-like symptoms, and CRP elevation, which necessitated drug suspension.

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CONFLICT OF INTERESTS

None.

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