

Antipsychotics, anticonvulsants, antiadrenergic agents and other drugs: what to do when posttraumatic stress disorder does not respond to selective serotonin reuptake inhibitors?

Antipsicóticos, anticonvulsivantes, antiadrenérgicos e outras drogas: o que fazer quando o transtorno do estresse pós-traumático não responde aos inibidores seletivos da recaptação da serotonina?

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Abstract

Objectives: In this narrative review, we aimed to describe different pharmacological strategies for the treatment of patients with posttraumatic stress disorder who display different levels of intolerance, resistance, and refractoriness to the treatment, or who are unable to take antidepressants, especially serotonin reuptake inhibitors. **Method:** We searched the ISI Web of Science and PubMed databases for original studies focusing on the treatment of posttraumatic stress disorder in different clinical scenarios. **Results:** Preliminary evidence pointed towards the efficacy of drugs such as risperidone, olanzapine, lamotrigine and prazosin as strategies to be employed in the above mentioned clinical scenarios. The choice of a specific "second line" drug should take into account not only symptoms, but also patterns of comorbidities, previous response to other treatments, pharmacological interactions, side-effects, and the patient's physical conditions. **Conclusions:** Future randomized controlled trials should be performed in order to unveil which drugs should be prescribed in the absence of adequate treatment and response to serotonin reuptake inhibitors.

Descriptors: Stress disorders, posttraumatic; Pharmacology; Clinical protocols; Review of the literature

Resumo

Objetivos: Nesta revisão narrativa, o objetivo foi descrever as opções farmacológicas para o tratamento do transtorno de estresse pós-traumático nos casos de intolerância, resistência, refratariedade ou impossibilidade de utilizar antidepressivos, especialmente inibidores seletivos da recaptação da serotonina. **Método:** Consulta às bases de dados ISI Web of Science e PubMed em busca de estudos originais sobre o tratamento farmacológico do transtorno de estresse pós-traumático em diferentes cenários clínicos. **Resultados:** Evidências preliminares apontam para a utilidade de drogas como a risperidona, a olanzapina, a lamotrigina e o prazosin como estratégias para o cenário clínico em tela. A escolha do medicamento de segunda linha deve levar em conta não só os sintomas, como também as comorbidades, os tratamentos prévios, as interações farmacológicas, os efeitos colaterais e as condições físicas do paciente. **Conclusões:** Futuros ensaios clínicos randomizados ainda são necessários para estabelecer com clareza alternativas farmacológicas aos antidepressivos para o tratamento do transtorno de estresse pós-traumático.

Descritores: Transtornos de estresse pós-traumáticos; Farmacologia; Protocolos clínicos; Literatura de revisão

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Introduction

The posttraumatic stress disorder (PTSD) is a severe response to a threat or to real events related to death or severe injury. The diagnosis of PTSD is associated with those individuals who present the following responses to these events: fear, horror or powerlessness, and who have, for at least one month, one reexperiencing symptom; three avoidance/numbing symptoms; and two hyperarousal symptoms. If the symptoms persist for more than three months, PTSD is considered to be chronic.¹

Although the use of antidepressants [mainly the serotonin selective reuptake inhibitors (SSRI)] is well-established in the treatment of PTSD, less than one third of the patients treated present an adequate response to the drugs.² In addition, there is still a large number of patients who do not tolerate the side-effects of the SSRI or have comorbid disorders that restrict its use (e.g.: bipolar mood disorder).

In the present study, we describe the main pharmacological alternatives for those patients with PTSD who do not show a satisfactory response to, who present intolerance to, or who are unable to take antidepressants.

Method

We searched the ISI Web of Science and PubMed databases for original studies on the alternatives to antidepressants for the pharmacological treatment of PTSD in different clinical scenarios.

Results

1. Atypical antipsychotics

Risperidone was used in the treatment of PTSD in at least five randomized clinical trials.³⁻⁷ In four of them, risperidone had superior results than placebo. In most of the studies, risperidone was added to the therapeutic scheme of the patients who had already been treated with other drugs. Risperidone was used as a monotherapy in only one study.⁶ Only the dimension of avoidance/numbing symptoms did not respond adequately to risperidone in the above mentioned studies. In open trials, most of them involving war veterans with chronic PTSD, risperidone showed to be useful for the decrease of episodes of waking up in the middle of the night and vivid dreams related to the trauma, with evident improvement during the three first weeks of treatment.⁸⁻¹⁰

Both randomized clinical trials with olanzapine used to treat PTSD presented different results.¹¹⁻¹² While in the study by Butterfield et al.¹¹ it was not possible to find a statistically significant difference between olanzapine and placebo in the treatment of PTSD non-related to war combat, Stein et al.¹² found higher results for olanzapine comparing to placebo in the eighth week of treatment involving war veterans with PTSD, with great improvement of sleep. In some open studies, the dimensions that presented the best responses to olanzapine were those of avoidance and hyperexcitability symptoms.^{13,14}

Although randomized clinical trials using quetiapine in the treatment of PTSD had not been found, quetiapine was efficient to decrease all dimensions of PTSD symptoms (mainly reexperiencing symptoms) in three open trials performed with civilians and military patients with PTSD.¹⁵⁻¹⁷ In one of these open studies, it was possible to identify clinical improvement in the second week of treatment. In a series of cases,¹⁸ quetiapine was proven to be efficient to decrease flashbacks in five patients with treatment-refractory PTSD using several classes of drugs.

The efficacy of clozapine was investigated in two studies involving patients with PTSD and comorbid psychotic disorders. In both studies, the use of clozapine was proven to be useful, although in the first study, an open trial with six adolescents,¹⁹ no specific PTSD instrument was administered and, in the second study, only a case of a war veteran was described.²⁰ Finally, the administration of aripiprazole to five war veterans with PTSD led to the decrease in the frequency of nightmares and improvement of the sleep pattern in four cases and worsening of the symptoms in the fifth patient.²¹

2. Anticonvulsants

Lamotrigine is a promising drug for PTSD treatment, with positive results in one randomized clinical trial. In this study, 11 civilian and military patients with PTSD²² were treated with lamotrigine or placebo. The group that used the drug presented a two-fold higher response rate than the placebo group, with special significance to the decrease of reexperiencing and avoidance/numbing symptoms.

The usefulness of the valproic acid in the PTSD treatment was assessed in six open trials,²³⁻²⁸ four of them involving war veteran samples, and two of them administered the drug as a monotherapy. In five of these studies, the valproic acid was associated with a decrease in the intensity of the three dimensions of PTSD symptoms. On the other hand, in another open trial,²⁸ in which the valproate was used as a monotherapy in the treatment of five civilian patients with chronic PTSD, no therapeutic response was found.

Carbamazepine was used in the treatment of PTSD in three open trials,²⁹⁻³¹ and one of them involved military patients. In these studies, carbamazepine resulted in significant decreases in the PTSD symptoms, mainly regarding impulsiveness, aggressiveness and reexperiencing.

Tiagabine was efficient to decrease PTSD symptoms in 26 civilians who were treated for 12 weeks.³² However, in the second phase of this study, the patients who had presented improvement with the treatment (i.e. 18) were split into one group that kept receiving the tiagabine treatment (10 patients) and another group that started getting placebo (eight patients). Curiously, the improvement achieved in the first phase of the study with tiagabine was maintained in both groups.

The usefulness of topiramate was assessed in a randomized clinical trial³³ with 38 civilians with chronic PTSD treated for 12 weeks. In this study, the number of patients who presented symptom remission was two-fold larger in the group that used topiramate than in the control group. However, topiramate led to a statistically significant decrease in the general PTSD symptoms in only one of the four scales applied. Topiramate was investigated in two other studies. In a study with 33 civilians with chronic PTSD,³⁴ the treatment with the anticonvulsant during four weeks led to a clinically significant improvement in 77% of the sample. In this study, the group of symptoms that presented a better response to the treatment was the group with reexperiencing symptoms. Topiramate also demonstrated to be useful for the decrease in the general PTSD symptomatology, mainly regarding the intrusive thoughts and nightmares in the open study with 35 civilian patients with chronic PTSD.³⁵

Other anticonvulsants were less often studied regarding PTSD, including levetiracetam, phenytoin and gabapentine. Levetiracetam was associated with antidepressants in 23 civilians with refractory chronic PTSD, resulting in a significant decrease in the symptoms.³⁶ Phenytoin led to a decrease in

the general PTSD symptoms, as well as social and functional improvement in nine patients with PTSD.³⁷ In a retrospective series of cases,³⁸ gabapentine demonstrated to be efficient in the treatment of insomnia and nightmares of 30 patients with PTSD.

3. Antiadrenergic agents

In a randomized clinical trial,³⁹ prazosin was significantly higher than placebo in the treatment of 10 war veterans with refractory chronic PTSD, with improvement of the general symptoms of the disorder (mainly regarding nightmares and sleep patterns). In an open trial⁴⁰ with 11 civilians with refractory PTSD, the association of prazosin in a single dose at night with its original prescriptions led to a significant decrease in the general PTSD symptoms. In another phase of the study, prazosin was also administered in the morning, which led to a new decrease in the disorders symptoms. All patients achieved a decrease in the disturbing dreams and dreams related to the trauma. Similarly, the treatment of eight war veterans and one Holocaust survivor with chronic PTSD led, in eight cases, to a significant decrease in the general PTSD symptoms, mainly regarding the nightmares related to the trauma.⁴¹ Similar findings were found in a retrospective study⁴² with 59 war veterans with refractory PTSD; that is, a significantly higher decrease in the nightmares in the groups of patients that used prazosin in comparison to those that did not take this drug. The use of prazosin for six months by five patients with refractory PTSD resulted in a significant decrease in the general PTSD symptoms and nightmares related to it.⁴³

Other antiadrenergic agents such as propranolol, guanfacine and clonidine have been less often studied in the PTSD treatment, although some results are promising. The administration of propranolol led to a significant decrease in the reexperiencing and hyperarousal symptoms in two studies, one performed with 12 veterans with chronic PTSD⁴⁴ and the other with 11 children with acute PTSD.⁴⁵ Guanfacine was investigated in a randomized clinical trial⁴⁶ and its administration did not result in a significant improvement of the PTSD symptoms if compared to the control group. The group treated with the drug presented a significantly larger number of side-effects. Finally, the use of clonidine patches in seven preschool children with PTSD led to the improvement of emotional lability, anger bursts, impulsivity, hyperexcitability, anxiety, hyperarousal, insomnia, opposition and nightmares in five children each, in addition to the great improvement in the aggressiveness symptoms in all children. However, the assessment was performed in a subjective manner by the children's physicians and teachers.⁴⁷

4. Opioid antagonists

The use of nalmefene in 18 war veterans with chronic PTSD resulted in the improvement of emotional numbing, flashbacks, nightmares, intrusive thoughts, anger and overreaction in eight patients.⁴⁸ The use of naltrexone for two weeks in seven patients with chronic PTSD led to a non-satisfactory clinical improvement of intrusive thoughts and hyperexcitability. All patients presented important side-effects, therefore, the administration of higher doses of the drugs were not possible.⁴⁹

5. Other drugs

The treatment of 16 patients with PTSD with cyproheptadine for one week did not show an improvement of sleep pattern and frequency of nightmares and was not well tolerated by the participants.⁵⁰ In another open trial, the use of dehydroepiandrosterone in five women with severe chronic PTSD resulted in the improvement of a wide variety of symptoms,

including dissociative symptoms, avoidance, numbing, reexperiencing, hyperarousal, anger, sadness or unstable mood and insomnia, in addition to an increase in the libido.⁵¹ The use of lithium in an open trial⁵² with five veterans with refractory PTSD also led to the decrease in anxiety, irritability, anger, and insomnia in all patients, although in one of them the association with propranolol was necessary. Although the results of the studies with dehydroepiandrosterone and lithium are promising, they must also be considered as preliminary since controlled clinical trials have not been performed yet.

Discussion

The antidepressants, particularly the SSRIs, are considered the first-choice drugs for the treatment of PTSD. However, with the lack of definitive algorithms for the treatment of PTSD, one question remains unanswered: what should we do when the SSRIs do not work, are not tolerated or cannot be administered? According to the data reviewed in the present study, there is preliminary evidence for the use of drugs such as risperidone, olanzapine, lamotrigine, and prazosin as strategies to be employed in this clinical scenario.

The atypical antipsychotics have proven to be useful for the treatment of the general PTSD symptomatology, mainly regarding insomnia, nightmares and flashbacks, and psychotic symptoms some times associated with PTSD. It is important to highlight, however, that the antipsychotics are not innocuous drugs, since they are associated with potentially severe complications such as tardive dyskinesia and metabolic syndrome. Therefore, these substances should not be regularly prescribed to patients with PTSD, only to those patients who are resistant or do not tolerate the conventional treatments. Furthermore, the physician must be concerned with the adequate follow-up of the patient, so that it can quickly identify and treat the complications caused by these drugs.

Although a relatively larger number of studies about the efficacy of the anticonvulsants in the treatment of resistant PTSD has been published, their methodological quality is lower than that of antipsychotics. Most of the studies reported improvement of the symptoms when the anticonvulsants were associated with traditional drugs. Gabapentine seems to be particularly efficient in the treatment of nightmares and flashbacks.

Prazosin is the only adrenergic antagonist presenting positive results in a randomized clinical trial with patients with refractory PTSD. In this study, prazosin was efficient in the treatment of reexperiencing symptoms, avoidant behavior, numbing and hyperarousal. The authors highlight the special efficacy of prazosin in the treatment of nightmares and sleep alterations.

It is important to make a comment here about the methodology used in the several studies reviewed. There is no consensus in the literature with the operationalization of concepts such as total remission, partial remission, resistance, and refractoriness of PTSD for the treatment in general. For example, while the response has been defined in a global manner, with a decrease higher or equal to 30% in the total score on the CAPS (one of the scales to screen and assess the severity of PTSD), the concepts of resistance and refractoriness have been inadequately treated as synonyms.

Conclusions

PTSD is a difficult to treat psychiatric disorder, especially when the patient does not tolerate or does not adequately respond to the antidepressants, particularly the SSRIs. According to the studies reviewed in the present work, there is preliminary evidence for the use of drugs such as risperidone, olanzapine, lamotrigine and prazosin as strategies to be employed in this clinical scenario. PTSD symptoms are heterogeneous and can respond in a specific manner to several drugs. The choice for a second line drug must take into consideration not only symptoms, but also comorbidities, previous treatments and pharmacological interactions, side-effects and the physical conditions of the patient.

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