PHARMACOTHERAPY OF POST-TRAUMATIC STRESS DISORDER

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ABSTRACT

Post-Traumatic Stress Disorder is a serious psychological disorder caused by an unexpected shocking event, such as sexual assault, warfare, serious injury or threat. However, being exposed to a traumatic experience does not automatically mean that a person will develop PTSD. It can be divided in two types. Type 1 results from a single trauma. Type 2 results from protracted and recurring trauma. PTSD is a pleomorphic disorder with symptoms in multiple domains (headache, pain, etc.) and perhaps for this reason (among others) combination treatments seem to be the standard in clinical practice. Effective treatments include both pharmacologic and psychosocial management. The principal goals of pharmacotherapy for PTSD should aim at 1) reducing core PTSD symptoms in all three clusters (re-experience, avoidance and numbing and increased arousal); 2) reducing functional impairment and disability; 3) improving life quality; 4) improving resilience to stress or trauma; 5) reducing co-morbidity such as depression, other anxiety disorders and substance abuse; 6) preventing relapse; and 7) preventing the development of PTSD in candidates who are at high risk of non-recovery after a trauma. Our review aimed to evaluate the available scientific data for pharmacological treatment in PTSD. Most studies involve antidepressants: selective serotonin reuptake inhibitors (SSRIs), selective noradrenalin reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and other serotonergic agents (trazodone and nefazodone). Antiadrenergic drugs tested include alpha-2 receptor agonists (clonidine and guanfacine) and the beta-receptor antagonist (propranolol). Other drugs tested include benzodiazepine, anxiolytics, antipsychotic agents and triptans for headache relief.

KEYWORDS: PTSD, treatment, options.
1. INTRODUCTION
Post-traumatic stress disorder (PTSD) is a chronic mental disorder that could unfold after exposure to an event or set of events with catastrophic nature, leading to severe physical and / or psychological trauma. Head trauma may result in headaches associated with a variety of structural lesions that may have serious sequelae, but most patients with post-traumatic headaches (PTHAs) attributable to concussions have no identifiable structural lesion. PTHAs are classified as secondary headache syndromes, as they follow trauma affecting the head, face, or neck. According to ICHD-2, acute PTHAs must begin within 7 days after head trauma or after regaining consciousness. Headaches that persist longer than 90 days from the initial trauma are classified as chronic PTHAs. The incidence of acute PTH following a concussion ranges from 31% to 96%. A review of 1,670 patients from 12 studies revealed that chronic headaches occur in 58% of patients with traumatic brain injury (TBI) of any severity.\[1\]

The most common traumatic events include death or physical, sexual or psychological threat that harm the victim or someone else in his presence.\[2\] PTSD is characterised by different symptom clusters, including intrusive/re-experiencing, avoidant/numbing and hyperarousal symptoms and it is possible that each is mediated by different neurobiological mechanisms, which may be normalised by specific pharmacological interventions. Certainly, there is growing evidence for rather specific dysregulations of neurotransmitter systems (including the serotonin, noradrenaline and dopamine systems) and neuroendocrine systems (including the hypothalamus-pituitary-adrenal axis), as well as for structural and functional neuranatomical abnormalities in PTSD.\[22\] Many of these pathways involved various in phases in the development of PTSD (Table 1).

2. Neural circuits and substrates involved in PTSD.
Conceptually PTSD can be viewed as maladaptation to traumatic stressor, to changing the terms of learning and attenuation, sensitivity and behavioral changes in the brain neurotransmitter systems related to these processes.

Factors associated with increased risk for development of PTSD include psychosocial factors and past trauma exposures, as well as genetic and epigenetic factors. PTSD is characterized by a range of neurobiological disruptions that may be responsive to medication, including changes in the hypothalamus–pituitary–adrenal axis, as well as alterations in the serotonergic and noradrenergic neurotransmitter systems.\[4\] Much of the literature currently focuses on
corticolymbic chain in PTSD with infringement in prefrontal cortex (PFC), hippocampus and amygdala in PTSD patients. PTSD has also been associated with abnormal hypothalamic-pituitary-adrenal axis markers as well as neural circuit abnormalities.\[5\] The hypothalamic-pituitary-adrenal (HPA) axis is the central coordinator of the mammalian neuroendocrine stress response systems and as such, is a major focus of scrutiny in patients with PTSD.\[8\] The amygdala, part of the limbic system within the temporal lobe, plays a primary role in threat detection and elaborating conditioned and unconditioned fear responses, including behavioral responses and activation of the HPA axis.\[6\] The hippocampus is implicated in the control of stress responses, declarative memory, and contextual aspects of fear conditioning. Not surprisingly, the hippocampus is one of the most plastic regions in the brain.

The medial prefrontal cortex (PFC) comprises the anterior cingulate cortex (ACC), subcallosal cortex and the medial frontal gyrus. Patients with PTSD exhibit decreased volumes of the frontal cortex, including reduced ACC volumes. This reduction in ACC volume has been correlated with PTSD symptom severity in some studies. In addition, an abnormal shape of the ACC, as well as a decrease of N-acetyl aspartate (NAA) levels in the ACC, has been reported for PTSD patients.\[7\]

GABA-ergic systems have been implicated in the pathogenesis of anxiety, depression and insomnia. These symptoms are part of the core and comorbid psychiatric disturbances in PTSD.\[8\]

Thus neurotransmitter systems that can be modulated as a pharmacological approach for the treatment of PTSD are serotonergic, noradrenergic, GABA-ergic and glutamatergic, since they affect the reactivity of the HPA axis. It is evident that pharmacological approaches can vary depending on whether the treatment is focused on the development of PTSD (preventive intervention in the period around the injury, which could lead to PTSD) or aims at the treatment of chronic PTSD.

**Table 1. Criteria for diagnosis and corresponding symptoms in PTSD.**

<table>
<thead>
<tr>
<th>Criterion</th>
<th>Symptom or Description</th>
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<tbody>
<tr>
<td>Criterion A: Trauma (both)</td>
<td>• Traumatic event that involved actual or threatened death, serious injury, or threat to physical integrity.</td>
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<td></td>
<td>• Intense response of fear, helplessness, or horror</td>
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<tr>
<td>Criterion B: Reexperiencing symptoms (one)</td>
<td>• Intrusive recollections of events</td>
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or more)  

| Criterion C: Persistent avoidance and numbing (three or more) | • Recurrent distressing dreams of the event  
| | • Acting or feeling as if the traumatic event were recurring  
| | • Distress at internal or external reminders of the trauma  
| | • Physiological reaction to internal or external reminders  
| Criterion D: Hyperarousal (two or more) | • Avoidance of thoughts, feelings, or conversations associated with trauma  
| | • Avoidance of activities, places, or people that arouse recollections of trauma  
| | • Failure to recall an important aspect of trauma  
| | • Loss of interest or participation in significant activities  
| | • Detachment from others  
| | • Restricted range of affect  
| | Lost sense of the future  
| Criterion E: Duration of disturbance | • Difficulty falling or staying asleep  
| | • Irritability or outburst of anger  
| | • Difficulty concentrating  
| | • Hypervigilance  
| | • Exaggerated startle response  
| Criterion F: Clinically significant distress or impairment | • Disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of function  


3. **Pharmacotherapeutic strategies in the treatment of PTSD**

The principal goals of pharmacotherapy for PTSD should aim at: 1) reducing core PTSD symptoms in all three clusters (re-experience, avoidance and numbing and increased arousal); 2) reducing functional impairment and disability; 3) improving life quality; 4) improving resilience to stress or trauma; 5) reducing co-morbidity such as depression, other anxiety disorders and substance abuse; 6) preventing relapse; and 7) preventing the development of PTSD in people who are at high risk of non-recovery after a trauma.\(^9\) The criteria for diagnosis and corresponding symptoms in PTSD are on Table 1.

Despite that theoretical principals, pharmacotherapy for PTSD has primarily been guided by empirical evidence that a specific drug has efficacy against a specific symptom. Indeed, at present, very few data in treatment of psychiatric disorders, including PTSD, link
psychobiological abnormalities to specific drug effects. In research and in clinical practice almost every class of psychotropic agent has been prescribed for PTSD patients. Most studies involve antidepressants: selective serotonin reuptake inhibitors (SSRIs), selective noradrenalin reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and other serotonergic agents (trazodone and nefazodone). Antiadrenergic drugs tested include alpha-2 receptor agonists (clonidine and guanfacine) and the beta-receptor antagonist (propranolol). Other drugs tested include benzodiazepine, anxiolytics and antipsychotic agents.

In the scientific literature there is sufficient evidence in favor of that PTSD is characterized by specific psychobiological dysfunctions, which in turn are of interest in the use of different drug classes in the treatment of trauma-associated biological effects.

Since PTSD is a chronic disorder, pharmacotherapy may continue for an indefinite period of time.\textsuperscript{[10]}

**Antidepressants**

Initial studies on the treatment of PTSD largely focused their attention on the different classes of antidepressants, particularly with the advent of new, more selective agents with improved safety profiles and tolerability as inhibitors of serotonin and noradrenalin reuptake. Studies on the efficacy of these drugs occupy much of the literature on treatment over the past 20 years.

Antidepressants with empirical support include monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs) and selective serotonin reuptake inhibitors (SSRIs). First-line agents include the SSRIs and the SNRI venlafaxine. These medications reduce the three core symptom clusters of PTSD: re-experiencing, hyperarousal and avoidance.

**Monoamine Oxidase Inhibitors (MAOIs)**

The MAOIs increase brain amine levels by interfering with their metabolism in the nerve endings, resulting in an increase in the vesicular stores of norepinephrine (NE) and 5-hydroxtryptamine (5-HT). When neuronal activity discharges the vesicles, increased amounts of the amines are released, presumably enhancing the actions of these neurotransmitters.\textsuperscript{[11]} The MAOI phenezine has been shown to be effective in PTSD.\textsuperscript{[14]} Phenelzine is a potent nonselective MAOI that exerts its clinical effects by elevating CNS
levels of the catecholamines 5-HT and GABA. The main obstacle in prescribing MAOIs is the strict dietary restriction in order to prevent the development of hypertensive crisis when taken in combination with foods that are rich in tyramine. Another risk is the development of serotonin syndrome when taken in combination with other serotonergic medications.\[^{12}\]

**Selective Serotonin Reuptake Inhibitors (SSRIs)**

The acute effect of SSRIs is a highly selective action on the serotonin transporter (SERT). SSRIs allosterically inhibit the transporter, binding at a site other than that of serotonin. They have minimal inhibitory effects on the NE transporter, or blocking actions on adrenergic and cholinergic receptors.\[^{11}\]

SSRIs can be recommended as a first-line treatment for PTSD. It has been hypothesized that the long term effect of antidepressants on mood and anxiety is related to the downregulation of the targeted serotonin synaptic receptors. Only sertraline and paroxetine have been approved for PTSD treatment by the FDA.\[^{13}\] SSRI have fewer side effects and greater safety than the other antidepressants but may produce insomnia, agitation, gastrointestinal symptoms and sexual dysfunction.\[^{14}\]

Some other SSRIs, such as citalopram and fluvoxamine, currently have far less evidence for their effectiveness in PTSD. All other agents are used in an off-label fashion.

Open label and double blind trials of sertraline, fluvoxamine, fluoxetine and paroxetine have established the SSRIs as the pharmacologic treatment of choice for PTSD. In general, SSRIs are fairly well tolerated and affect a wide range of PTSD symptoms. Effects typically begin at 4 to 6 weeks; with full effects reached in some cases after 10 to 12 weeks or longer. In a continuation study of sertraline in PTSD, Londborg et al., reported that some patients may require 24 weeks or longer at a full SSRI dose to obtain maximum benefit.

**Selective Noradrenaline Reuptake Inhibitors (SNRIs)**

SNRIs bind to transporters for both serotonin and NE, presumably enhancing the actions of both neurotransmitters. The SNRIs differ from the TCAs in lacking significant blocking effects on peripheral receptors including histamine H1, muscarinic, or α-adrenergic receptors.\[^{11}\] Like fluoxetine, the SNRI venlafaxine is not approved for the treatment of PTSD, but it is often used off-label as first-line monotherapy in these patients. Venlafaxine acts primarily as a serotonin reuptake inhibitor (SRI) at lower doses and as a combined
serotonin–norepinephrine reuptake inhibitor (SNRI) at higher doses. Extended-release (ER) venlafaxine was shown to be effective in two trials involving more than 800 patients with non–combat-related PTSD. Venlafaxine ER differed significantly from placebo in improving hyperarousal. Its mechanism of action is believed to be associated with its potentiation of neurotransmitter activity in the CNS. Preclinical studies have shown that venlafaxine is a potent inhibitor of neuronal serotonin and norepinephrine reuptake and weak inhibitors of dopamine reuptake.

![Fig.1 Treatment of Posttraumatic Stress Disorder With Venlafaxine ER: A 6-Month Randomized Controlled Trial. Davidson J, Baldwin D et al. 2006.](image)

**Atypical antidepressants**

Mirtazapine is a noradrenergic and specific serotonergic antidepressant that is approved in many countries for the treatment of major depression. Mirtazapine potentiates noradrenergic and 5-HT1A-mediated serotonergic neurotransmission via antagonism of central a2-adrenergic auto- and heteroreceptors and postsynaptic blockade of 5-HT2 and 5-HT3 receptors. Mirtazapine does not inhibit the reuptake of serotonin and noradrenaline. It has a low affinity for dopaminergic receptors, while it is a potent antagonist of H1 receptors and a moderate antagonist at muscarinic receptors.

In the placebo-controlled trial, mirtazapine was more effective than placebo on some measures in PTSD and general anxiety symptoms, but both mirtazapine and placebo showed
beneficial effect. Mirtazapine has a favorable effect on sleep and a modest potential for drug interactions with absence of serious adverse effects.\[^{12}\]

Nefazodone is defined as 5HT2a receptor antagonist with some affinity for the α adrenergic receptor and 5HT1a. Its half-live is short and usually require administration 2 or 3 times daily.\[^{11}\] It has been helpful in PTSD and can also target hyperarousal symptoms, such as sleep disturbance and anxiety. It carries potential for possible liver failure, which has occurred in about 1:300,000 cases. It is important to monitor liver functions and to consider nefazodone’s use with caution when the patient uses other medications or substances that may irritate the liver, such as statins, divalproex, or large quantities of alcohol. Nefazodone is a potent inhibitor of cytochrome P450–3A4 and will raise blood levels of atorvastatin and other statin drugs, increasing the risk of rhabdomyolysis; patients receiving atorvastatin must be switched to a statin with fewer potential interactions before receiving nefazodone.\[^{17}\]

**Alpha adrenergic blockers**

Prazosin is the most lipid soluble of the available α 1 – receptor antagonists. It enters the brain easily from the blood and is centrally active. Its effects seem to result from a selective, competitive inhibition of α 1 -adrenergic receptors and it generally causes no change in heart rate, cardiac output, renal blood flow, and glomerular filtration rate.\[^{18}\]

Prazosin has proved to be an effective treatment for PTSD-related nightmares. While the specific mechanism by which prazosin decreases nightmares is unknown, it is hypothesized that by blocking the alpha-1 receptor in the central nervous system, prazosin decreases nightmares that result from increased adrenergic responsiveness in PTSD. It blocks the effects of norepinephrine release from noradrenergic neurons, such as those originating within the locus ceruleus of the brainstem. Despite prazosin’s established usefulness for reducing nightmares, results have been mixed regarding its efficacy for the full PTSD syndrome.\[^{14}\] Hypotension is the main side effect to monitor when initiating prazosin. Although this has not proven to be a problem for most patients receiving this medication a slow titration is recommended for patients without comorbid hypertension.\[^{17}\] A recent comparison study of prazosin and quetiapine for ameliorating night-time sleep disturbance indicates better overall tolerability of prazosin.\[^{20}\] It also stimulates the secretion of the corticotropin-releasing factor (CRF) that has anxiogenic properties, disrupts sleep and favours the emergence of basic alarm-related cognitive processing.\[^{18}\]
Clonidine a noradrenergic α2 agonist, has shown some beneficial effects in decreasing PTSD-associated symptoms of explosiveness, sleep problems, nightmares, startle, hyperalertness, and intrusive thinking.[12]

**Fig. 2 Prazosin Effects on Objective Sleep Measures and Clinical Symptoms in Civilian Trauma Posttraumatic Stress Disorder: A Placebo-Controlled Study. Taylor F, Martin P, et al. 2008.**

**Benzodiazepines**

Benzodiazepines enhance activity of GABA binding do the GABA-A receptor which produces CNS depression.[13] Although the benzodiazepines belong to the anxiolytic class of medications and are widely used for symptomatic relief of insomnia, panic, anxiety and irritability, their use should be discouraged in PTSD due to the lack of evidence for their effectiveness in reducing PTSD core symptoms. The risks associated with their use are outweigh and drug tolerance.[12] Any acute use should be short term (e.g., no more than five days) with frequent re-evaluation for side effects.[13]

Examples of commonly used benzodiazepines are: Lorazepam, Clonazepam, Alprazolam, Diazepam.

**Antipsychotic Agents**

Older drugs have high affinity for dopamine D2 receptors, whereas newer antipsychotic drugs have greater affinity for serotonin 5-HT2 receptors.[11]

Antipsychotics are supposed to ameliorate PTSD symptoms by acting on serotonergic and
dopaminergic systems, both of which have been implicated in the pathogenesis of PTSD.

Three randomized clinical trials (RCTs) exploring the efficacy of risperidone as an adjunctive treatment to antidepressants showed that it was superior to placebo in decreasing the severity of PTSD symptoms but did not find risperidone to be effective in alleviating avoidant behavior or emotional numbness.\(^{19}\) In the only double-blind placebo-controlled trial of quetiapine for PTSD, Hamner et al. (2003) demonstrated in a 12 week monotherapy trial for 80 patients with PTSD a significant reduction in PTSD symptoms with quetiapine over placebo, especially in re-experiencing and hyper arousal. The earlier open label studies of quetiapine as an adjunctive treatment for PTSD had shown significant improvement in PTSD symptoms with quetiapine.\(^{19}\)

Although second-generation (atypical) antipsychotic agents were originally developed to treat psychotic disorders, they are also used in patients with other psychiatric disorders, including PTSD. These drugs act primarily on the dopaminergic and serotonergic systems. Clinical studies have indicated that they are useful in ameliorating psychotic symptoms in patients with PTSD.\(^{15}\)

These drugs (thioridazine/clozapine/risperidone) cannot be recommended for routine use in PTSD because only a few clinical trials indicating their effectiveness have been published. They may ultimately prove to have a unique role for patients who are refractory to first- and second-line drugs—especially when these patients exhibit extreme hypervigilance, paranoid symptoms, agitation, or psychosis. They have many side effects, some of which are serious.\(^{14}\)

**Mood stabilizers for PTSD**

The possibility that limbic hypersensitization or kindling might underlie increased arousal to traumatic stimuli in PTSD suggests that anticonvulsants might be effective in treating this disorder.\(^{4}\) The primary benefit of using the anticonvulsant mood stabilizers lies in the treatment of co-occurring PTSD and bipolar disorder.\(^{20}\) These medications, affect the balance between the excitatory neurotransmitter glutamate the most common neurotransmitter in the central nervous system and the inhibitory neurotransmitter GABA by acting indirectly to affect these neurons when their neuronal receptor sites are activated.\(^{13}\) The existing evidence does not support the use of anticonvulsants as monotherapy for the management of PTSD core symptoms, but they are frequently used as adjunctive
treatments.\textsuperscript{[12]} Most of the studies have been conducted with topiramate, lamotrigine, carbamazepine, valproate, and gabapentin.\textsuperscript{[20]}

\textit{The role of psychotherapy in the treatment of PTSD}

Psychotherapy, behavioral interventions and use of different first-line agents are the best approach supported by the available evidence and are recommended in the 2010 revision to the Clinical Practice Guideline (CPG).

Second-line agents can be considered as the next treatment step if these first-line agents are not effective in treatment.\textsuperscript{[17]}

\textbf{Pharmacotherapy of Post-traumatic headache (PTH)}

A multidisciplinary approach is stressed in the treatment of PTH due to the multitude of associated symptoms. Prophylactic therapies for a migraine or tension-type presentation include the standard approach with β-blockers, antidepressants, or antiepileptic drugs. For acute attacks and exacerbations, NSAIDs, simple analgesics and triptans are usual firstline options depending upon the headache type. Loder and Biondi, (2002) reported botulinum toxin injections as efficacious for chronic PTH.\textsuperscript{[22]} The migraine-specific triptans have revolutionized the treatment of migraine and are usually the drugs of choice to treat a migraine attack in progress. Triptans act at the cellular level by activating 5HT1B/1D and in some cases 5HT1F receptors. The best recognized mechanism of action of triptans is vasoconstriction (a mechanism targeted since vasodilation has long been thought to contribute to migraine)\textsuperscript{[23]} and decrease neurogenic inflammation as well as reducing central nociception.\textsuperscript{[24]}

\textbf{CONCLUSION}

Finally it is important to note that vulnerability factors, such as prior traumas or genetic variations, may be important for elucidating heterogeneity in PTSD and thinking about more appropriate treatment approaches. Furthermore, PTSD is often co-morbid with other psychiatric disorders (depression and/or substance abuse), which may require additional treatments, thus a careful evaluation is warranted and the choice of a medication should always take into consideration the associated co-morbidities, the history of previous treatment trials, the possibility of drug interactions, the occurrence of side effects and the physical and psychological conditions of the patient. Continued research into PTSD biomarkers, genetics,
as well as basic studies of the neurobiology of PTSD-relevant processes is critical to improving pharmacological, psychosocial and combination therapies.

They're is no potential conflict of interest.

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REFERENCES


