The pharmacological prevention of Post-traumatic Stress Disorder

LÁSZLÓ PÉTER

State Health Center, Psychiatry Department, Budapest, Hungary

Post-traumatic Stress Disorder (PTSD) affects a significant portion of population: with 6–8% lifetime prevalence. PTSD is a common reaction to traumatic events. Many people recover in a few months following trauma, but in a significant group of the patients the symptoms persist, often for years. Key symptoms of PTSD such as intrusion (like flashbacks, nightmares), avoidance (people, situations remembering to the trauma) and hyperarousal (sleeplessness, irritability, concentration difficulties) cause significant disability. The comorbidity with depression, anxiety disorders, drug-alcohol abuse could increase the burden of disease as well. The aim of this review is to present pharmacological methods and possibilities which are able to help to prevent the developing of PTSD, and to give a brief summary of results and effectiveness of the pharmacological preventive methods. There are a lot of models of pathogenesis of PTSD, but the most accepted is the noradrenergic hypothesis. A traumatic event overstimulates endogenous stress hormones, which mediates an overconsolidation of the event’s memory trace. Recall of the event in response to reminders releases further stress hormones, that cause further overconsolidation, and the overconsolidated memory generates PTSD symptoms. Noradrenergic hyperactivity in the basolateral amygdala is hypothesized to mediate this cycle. Every drugs which can break this process, could be a potential prevention drugs. The beta-adrenerg antagonists such as propranolol are blocking post-synaptic norepinephrine receptors in the basolateral amygdala. Two clinical and two non-clinical studies suggest that posttrauma propranolol reduces subsequent PTSD. Alfa2-adrenergic agonists and opioids are preventing pre-synaptic norepinephrine release. There have been a few trials of alfa2-adrenergic agonists. A retrospective study of morphine treatment of burned children showed, that treatment of morphine reduced the symptoms of PTSD. Few studies did not find the benzodiazepines effective in preventing PTSD. Cortisol both enhances memory consolidation, and reduces memory retrieval, leading to mixed predictions. Few controlled studies found that cortisol reduced PTSD. Selective serotonin reuptake inhibitors (SSRIs), antiepileptics have yet to be tried. The staff of Hungarian Defence Forces performing their duties, which result from the Constitution and the NATO, could get to extreme and traumatic stress situations. It is important to inform the military doctors and the commanding officers as well about the safety and inexpensive pharmacological possibilities of the prevention of PTSD.
Introduction

Posttraumatic stress disorder is a serious public mental health problem. The National Comorbidity Survey estimated the life-time prevalence of PTSD in the US at 7.8%. The life-time prevalence among Vietnam veterans were estimated at 31%! The diagnosis of PTSD requires exposure to an extreme stressor and a characteristic set of symptoms that have lasted for at least 1 month.

What is an extreme stressor?

- Serious accident or natural disaster
- Rape or criminal assault
- Combat exposure
- Child sexual or physical abuse or severe neglect
- Hostage/inprisonment/torture/displacement as refugee
- Witnessing a traumatic event
- Sudden unexpected death of loves one

The person has the following three main types of symptoms:

Re-experiencing of the traumatic event as indicated by:

- Intrusive distressing recollections of the event
- Flashbacks (feeling as if the event were recurring while awake)
- Nightmares (the event or other frightening images recur frequently in dreams)
- Exaggerated emotional and physical reactions to triggers that remind the person of the event.

Avoidance and emotional numbing as indicated by:

- Extensive avoidance of activities, places, thoughts, feelings, or conversations related to the trauma
- Loss of interest
- Feeling detached from others
- Restricted emotions

Increased arousal as indicated by:

- Difficulty sleeping
- Irritability or outbursts of anger
- Difficulty concentrating
- Hypervigilance
- An exaggerated startle response
In the first 2–3 days after a traumatic event acute stress reaction can develop. After that, between 2 and 30 days of posttrauma the symptoms of acute stress disease can appear. And if the symptoms consist 1 month after the trauma we can only say about PTSD. The comorbidity rate is really high, 80–90% in chronic PTSD. The high comorbidity rate is responsible for diagnostic problems, because the high rate of parallel psychiatric and somatic diseases could cover the symptoms of PTSD, so the adequate treatment could be delayed. This high comorbidity increases the costs of health, worsens quality of life, and reduces the lifetime of patients suffering from PTSD. All doctors, mainly in general practice, should recognize the occurrence of PTSD. They need to realize the chronicity of PTSD.

Primer prevention of PTSD involves the prevention of traumatic events. Secondary prevention means intervening in the aftermath of a traumatic event to forestall the development of PTSD. Tertiary prevention is responsible for interventions designed to reduce symptomatology and disability after PTSD has developed. Until recently, the most popular secondary preventive intervention for PTSD was psychological debriefing. However recent reviews of controlled studies have failed to confirm its efficacy. Routine debriefing following traumatic events is not recommended.1

An important question, that when do we start the preventing interventions. A study that employed positron emission tomography in humans found that it takes 6 hours to permanently store the memory of a newly learned skill in the brain.2 So as soon as possible we have to start the treatment, to prevent a subsequent development of PTSD (Figure 1).

Figure 1. Time of prevention of PTSD

There are a lot of models of pathogenesis of PTSD, and maybe the most accepted is the noradrenergic hypothesis. But the serotonergic area, the dopaminergic-opioid system, the hypothalamo-pituitary-adrenocortical (HPA) axis, and the hippocampal memory deficit are responsible for the development of PTSD. A traumatic event
overstimulates endogenous stress hormones, like epinephrin, vasopressin, hydrocortisone, ACTH, that mediates overconsolidation of the event’s memory trace. Recall of the event response to reminders releases further stress hormones, that cause further overconsolidation, and the overconsolidated memory generates PTSD symptoms. Noradrenergic hyperactivity in the basolateral amygdala is hypothesised to mediate this cycle. Every drug which can break this process could be a potential preventing drug\(^3\) (Figure 2).

**Drugs acting on human adrenerg system**

*Decreasing andrenergic-noradrenergic level (B-blocking, L2-agonists, opioids)*

How can we confirm the association the higher heart rate, hyperadrenergic state and the development of PTSD. Shalev investigated 86 trauma survivors, who were arrived at the emergency department. 20 subjects met PTSD diagnostic criteria at the 4-month assessment. Between them the heart rate was higher after the trauma, but not after 1 and 4 month. Elevated heart rate shortly after trauma is associated with the later development of PTSD.\(^4\)

If we can accept, that after a traumatic event there is a hyperadrenergic state, it is obvious that beta blockers can mediate this process. The beta-adrenerg antagonists such
as propranolol blocks post-synaptic norepinephrin receptors in the basolateral amygdala. Two clinical and two non-clinical studies suggest that posttrauma propranolol given after trauma reduces subsequent PTSD. Only propranolol is effective, because other beta-blockers do not cross the blood-brain barrier.

Substantial evidence from animal research indicates that enhanced memory associated with emotional experiences involves activation of the B-adrenergic system. To examine this implication in human subjects Cahill and colleagues investigated the effect of the beta-adrenergic receptor antagonist propranolol on long-term memory for emotionally arousing short story, or a closely matched, but more emotionally neutral story. There was a randomization period, and after that the first group got 40 mg propranolol, while the others got placebo. After that they watched the slide show. 1 week later they were tested with a surprise memory test. The propranolol significantly impaired memory of the emotionally arousing story, but did not affect memory of the emotionally neutral story.5

In another study van Stegeren and colleagues compared the effects of propranolol, a lipid soluble drug, which crosses the blood-brain barrier easily, with those of nadolol, a water soluble drug which crosses the blood-brain barrier to a considerably lesser extent, to determine whether the effect involved peripheral or central B-adrenergic receptors. The effects of these drugs taken before subjects watched a slide show that was either emotionally arousing or relatively neutral in content, and were tested 1 week later with a surprise memory test. Consistent with previous results propranolol impaired memory in the subjects who saw the emotional version of slide show. In contrast nadolol did not impair memory of the emotional slide show. These results indicate that the blockade of central B-adrenergic receptors is responsible for the reduction in storage of emotional events.6

The first clinical study by Pitman and colleagues recruited 41 patients who presented to a general hospital emergency room immediately following a traumatic event (mostly motor vehicle accidents) All patients had to meet the current diagnostic criteria for PTSD, and had to have a pulse rate higher than 80 beats per minute, indicative of a hyperadrenergic state. The patients were randomized to receive a course of oral propranolol 40 mg or placebo four times daily for 10 days, followed by a 9-day medication taper period. The first dose of study medication was administered an average of 4 hours after the traumatic event’s occurrence. One-month posttrauma total scores of CAPS showed a trend to be lower in the 21 completers of the course of study medication who had received propranolol, compared with the 20 completers who had not.7

In another controlled, non-blind, non-randomized study by Vaiva and colleagues recruited 19 patients with a high pulse rate from two emergency department in France,
2–20 hours following an motor vehicle accidents or physical assault. From the 19 patients 11 got propranolol, while the other 8 refused propranolol, but agreed to participate in the study. The dose of propranolol was 40 mg three times a day. At two months posttrauma, levels of PTSD symptoms were significantly lower in the patients treated with propranolol.8

Propranolol was studied in two small trials among adults with PTSD, where the propranolol was given continuously for months. Kolb and associates treated 9 Vietnam veterans and noted reduced trauma-related nightmares, intrusive memories, hypervigilance, startle response, and expression of anger.9 However Kinzie reported that propranolol was not helpful in a sample of Cambodian refugees with PTSD.10 So the results are not unequivocal.

Another approach to blocking the potentiation of the consolidation of a traumatic memory would be to give pharmacologic agents that act pre-synaptically to reduce norepinephrin release. Candidate drugs for this purpose include opioids (morphins) and alpha 2 adrenergic agonists, (like clonidine and guanfacin).

Saxe and colleagues performed a study of relationship between the amounts of morphine given to severely burned children and the children’s PTSD symptoms. The children who received higher doses of morphine had a greater reduction in PTSD symptoms over a 6-months hospital stay. The opioids seems to be effective in preventing PTSD, but difficult to implement due their addictive potential.11

There were a few study with clonidine, which inhibits the function of cells of locus coerulei, also reduce the release of norepinephrin. PTSD in abused and neglected preschool children often leads to extreme and disabling symptoms, that require a highly structured treatment program. Harmon’s results indicate that clonidine is effecting in reducing symptoms of aggression, hyperarousal and sleep difficulties in children with severe PTSD. However caution is advised when using psychotropic medication in preschool children.12

*Increasing adrenergic-noradrenergic level (cortisol)*

Cortisol both enhances memory consolidation and reduces memory retrieval, attenuate the positive feed-back, leading to mixed predictions. Two studies have found that lower posttrauma cortisol levels predict subsequent PTSD. In the first study motor vehicle accident victims who subsequently were diagnosed with PTSD had lower plasma cortisol levels 30 minutes after their accident compared to a control group.13

Delahanty and colleagues examined the relationship between initial urinary hormone levels and subsequent PTSD symptoms in 99 motor vehicle accident victims, who arrived to a trauma unit. The urine was collected for the next 15 hours after trauma.
Victims who subsequently met acute PTSD diagnostic criteria 1 month after accident had significantly lower cortisol excretion in the immediate aftermath of the accident than victims who did not meet diagnostic criteria.\textsuperscript{14} Table 1 shows we give hydrocortisone after a traumatic events can we prevent the development of PTSD.

<table>
<thead>
<tr>
<th>motor vehicle accident</th>
<th>trauma</th>
<th>motor vehicle accident</th>
</tr>
</thead>
<tbody>
<tr>
<td>anonymous</td>
<td>number of patients</td>
<td>n = 99</td>
</tr>
<tr>
<td>after 30 minutes of trauma</td>
<td>plasma cortisol level</td>
<td>have not measured</td>
</tr>
<tr>
<td>have not measured</td>
<td>urinary cortisol level</td>
<td>collect for 15 hours after trauma</td>
</tr>
<tr>
<td>significantly lower cortisol level</td>
<td>PTSD</td>
<td>significantly lower cortisol level</td>
</tr>
</tbody>
</table>

Schelling and colleagues have found that exogenously given cortisol reduce the development of subsequent PTSD in medical-surgical patients. An initial retrospective case-control analysis revealed that septic shock patients who received hydrocortisone 100 mg bolus during the sepsis episode followed by 0.18 mg/kg/hour until shock reversal had a significantly lower subsequent incidence of PTSD, than patients who received standard treatment for their septic shock. These findings were replicated in a randomized, double-blind study. During a sepsis episode 11 patients were randomly assigned to receive placebo, and nine were assigned the above mentioned dose of hydrocortisone for 6 days. Results revealed that only 1 of 9 from the hydrocortisone group, but 7 of 11 from the placebo group met PTSD criteria assessed 31 month after discharge from the intensive care unit.\textsuperscript{15}

Schelling and colleagues examined the efficacy of peri- and post-operative exogenous hydrocortisone in preventing PTSD symptoms in patients following cardiac surgery. Twenty six patients received a loading dose of hydrocortisone 100 mg followed by a continuous infusion 10 mg/hour during post-operative day. Twenty two comparison patients received standard treatment. Results revealed that the patients who received the hydrocortisone regimen reported significantly fewer PTSD symptoms than comparison patients\textsuperscript{16} (Table 2).
Table 2. Use of hydrocortisone in prevention of PTSD

<table>
<thead>
<tr>
<th>Use of hydrocortisone in prevention of PTSD</th>
</tr>
</thead>
<tbody>
<tr>
<td>septic shock</td>
</tr>
<tr>
<td>n = 20</td>
</tr>
<tr>
<td>hidrocortisone (9) or placebo (11)</td>
</tr>
<tr>
<td>100 mg in bolus, then 0.18 mg/kg/hour</td>
</tr>
<tr>
<td>6 days</td>
</tr>
<tr>
<td>significantly fewer PTSD symptoms in group of hidrocortisone</td>
</tr>
</tbody>
</table>

Other possibilities

Beside noradrenergic hypothesis there are at least two other models of PTSD pathogenesis. For example the neurophysiological kindling model of PTSD suggest anti-kindling agents in addition to having some therapeutic value, may also have preventive value. There were some studies with carbamazepine (CBZ), which is originally an antiepileptic drug, but it is effective as a mood-stabilizer and antiaggressive drug too. After a traumatic event, in patients who got carbamazepine, the number of flashback episode, irritability and aggression was reduced too.

Another model of PTSD, the stress and hidrocortisone induced neurotoxicity model suggest that drugs have been found to block stress-induced hippocampal damage, including antiepileptics, selective serotonin reuptake inhibitor (SSRI) and possibly even anti-cortisol drugs mifepriston may also be useful in preventing PTSD.

We have to say about the GABA agents, which oppose norepinephrine action in the baso-lateral amygdala (BLA). Benzodiazepine (BZD) would appear to be a good choice for the preventing and treatment of PTSD. However, BZD are ineffective. In an Israeli nonrandomized trial of accident and terrorism survivors, patients who received alprazolam or clonazepam were compared with a group who received no BZD. The 13 patients who received a benzodiazepine did not experience fewer symptoms of PTSD than the 13 control subjects. At six month follow-up, in the benzodiazepine group had higher rates of PTSD. We have to say about the dependency and tolerance too of benzodiazepine. The general use of BZD is not suggested. Trials of newer GABA-agents like gabapentine or tiagabine are indicated.
Conclusion

After a traumatic event has to make an early intervention because in 6 hours permanently store the memory of a newly learned skill in the brain. More studies verified that propranolol seems to be effective. The hydrocortisone, clonidine, opiates and carbamazepine functions are not unequivocal, but the results are hopeful. There are no known psychotherapy methods. The most popular secondary preventive intervention for PTSD was psychological debriefing, but it is not effective. Therefore the routine debriefing following traumatic events is not recommended. Need to be further investigations in future, to decide, that can we prevent the development of PTSD by a pharmacological way.

We can say that the propranolol is effective in the prevention of PTSD. It is cheap, world-wide available, so why don’t we use it? The commanders, and the medical staff have to think the possibility of PTSD after a traumatic event, and if they give propranolol to soldiers in the first few hours post-trauma, maybe prevent of the development of PTSD.

References

3. PITMAN, R.K., DELAHANTY, D., 2005: Conceptually Driven Pharmacologic Approaches to Acute Trauma. CNS Spectrums, 10 (2): 99–106