

# Posttraumatic stress disorder: From pathophysiology to pharmacology

Bilge Togay, MD, and Rif S. El-Mallakh, MD

**P**osttraumatic stress disorder (PTSD) occurs acutely and chronically in the aftermath of severe and potentially life-threatening trauma.<sup>1</sup> The prevalence of PTSD varies significantly across countries and by type of trauma (*Box*,<sup>1-7</sup> page 34).

Individuals who develop PTSD experience a wide range of symptoms.<sup>8</sup> These can be categorized as PTSD-specific symptoms, or nonspecific symptoms. PTSD-specific symptoms include nightmares, flashbacks, dissociative reactions, hyperreactivity or hyperarousal, distress with reminders of trauma, and avoidance of trauma-related physical reminders and thoughts/feelings (*Table*,<sup>8</sup> page 35). Nonspecific symptoms include depressive and anxiety symptoms and significant problems in social, relationship, or work situations.<sup>8</sup>

While successful treatment necessitates taking all of these symptoms into account, understanding the pathophysiology of PTSD can inform a more focused and rational treatment approach. In this article, we describe some key pathophysiologic PTSD studies, and focus on PTSD-specific psychopathology to inform treatment.

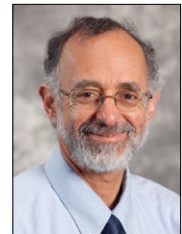
## Brain systems implicated in PTSD

**Neuropeptide Y** (NPY) is an anxiolytic endogenous peptide that has connections to the hypothalamic-pituitary-adrenal (HPA) axis. Its levels can be modulated by stress.<sup>9</sup> Preclinical and clinical studies strongly support a potential role of NPY dysfunction in the pathophysiology of PTSD. Lower concentrations of NPY increase susceptibility to PTSD in combat veterans<sup>10</sup> and in

animal models.<sup>11</sup> Three single-nucleotide polymorphisms (SNPs) appear to mediate this effect.<sup>12</sup> These findings strongly support pharmaceutical targeting this system as a useful therapeutic approach.<sup>13,14</sup> Indeed, intranasal NPY administered as a single dose reduces anxiety in animal models<sup>15</sup> and in humans,<sup>16</sup> but this work has not yet translated into clinical tools.

**Corticotropin-releasing hormone receptor (CRHR1) gene.** Corticotropin-releasing hormone has been implicated in PTSD.<sup>17</sup> Corticotropin-releasing hormone receptors (CRHR) are important mediators in response to stress.<sup>18,19</sup> They bind corticotropin-releasing hormone and contribute to the integration of autonomic, behavioral, and immune responses to stress.<sup>20</sup> Single-nucleotide polymorphisms in the regulatory portion of the *CRHR1* gene are associated with an increased risk for depression in adults who have a history of child abuse.<sup>21</sup>

The *CRHR1* receptor antagonist GSK561679 is an investigational agent for the treatment of mood and anxiety disorders.<sup>22</sup> In exploratory studies,<sup>23,24</sup> GSK561679 was found to inhibit fear-potentiated startle in patients with PTSD, but not overall PTSD symptoms, although a subset of women with



Rif S. El-Mallakh, MD  
Department Editor

Dr. Togay is a Visiting Researcher, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, Kentucky. Dr. El-Mallakh is Professor and Director, Mood Disorders Research Program, Department of Psychiatry and Behavioral Sciences, University of Louisville School of Medicine, Louisville, Kentucky.

### Disclosures

Dr. Togay is a speaker for Lundbeck, Janssen, Otsuka, Indivior, Sage, Teva, and Takeda. Dr. El-Mallakh is a speaker for Lundbeck, Janssen, Otsuka, Indivior, Sage, Teva, and Takeda.



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## Clinical Point

For patients with PTSD and the short form of 5-HTTLPR, antidepressants may actually worsen fear response

### Box

## The prevalence of PTSD

In the general population, the prevalence of posttraumatic stress disorder (PTSD) varies from as low as 0.3% in China to as high as 6.1% in New Zealand<sup>1</sup> and 6.8% in the United States.<sup>2</sup> These rates are actually much lower than expected when one considers that severe trauma is experienced by 60.7% of men and 51.2% of women.<sup>3,4</sup> Although the majority of individuals exposed to trauma experience emotional distress immediately following a traumatic event, most of them do not develop PTSD.<sup>5</sup>

It appears that the context of trauma is important: 12% to 15% of veterans experience PTSD, compared with 19% to 75% of crime victims and 80% of rape victims.<sup>1</sup> The lifetime risk for PTSD is twice as high in women as it is in men,<sup>6</sup> and genetic vulnerability may play a role. For example, twin studies showed that approximately 30% of the risk for PTSD may be mediated by genetic predisposition.<sup>7</sup>

a specific genetic variant of the *CRHR1* gene (rs110402) experienced significant benefit.<sup>25,26</sup> This suggests that we must learn more about this system before we proceed.<sup>27</sup>

**Brain-derived neurotrophic factor (BDNF).** The synthesis of BDNF is influenced by neuronal activity in the brain and plays a role in synaptic transmission and plasticity.<sup>28</sup> Brain-derived neurotrophic factor is encoded by the *BDNF* gene, which has been implicated in stress vulnerability.<sup>29</sup> A common SNP in the pro-region of the human *BDNF* gene results in a valine-to-methionine substitution at the 66th amino acid (Val66Met). The functional Val66Met polymorphism may have a role in the risk of developing PTSD. However, not all studies support this finding. One study found that an SNP with a resulting Val66Met polymorphism is associated with adult PTSD symptoms after childhood abuse, while a meta-analysis of 7 studies did not confirm this.<sup>30,31</sup> We need to learn more about BDNF before we proceed.<sup>32</sup>

## Serotonin transporter (5-HTT) gene.

Serotonin transporter is a monoamine transporter protein that terminates the neurotransmitter signal by transporting serotonin from the synaptic cleft back into the presynaptic neuron. It is encoded by the *SLC6A4* gene, which resides on the long arm of chromosome 17(17q11.1-q12). It is a large gene with 31 kilo bases and 14 separate exons (transcribed regions).<sup>33,34</sup>

This gene has several variants. The best-studied is a variation in the promoter region. A 44-bp insertion or deletion yields the “long” and “short” alleles, respectively. The proteins produced by the 2 alleles are identical, but the amount of expressed protein is different. The short allele (“S”) is associated with a nearly 50% reduction in 5-HTT expression in both homozygotes and heterozygotes.<sup>35</sup> A greater incidence of serotonin transporter promoter region (5-HTTLPR) S has been found in individuals with PTSD compared with those without PTSD,<sup>36-38</sup> and 5-HTTLPR S increases the risk of PTSD in individuals with low social support<sup>39</sup> or after very few traumatic events.<sup>40</sup> The short allele variant is also associated with depression in individuals who face adversity.<sup>35,41</sup>

The overrepresentation of the short form of 5-HTTLPR in individuals who develop PTSD may represent a potential problem with current treatment paradigms, in which an antidepressant is the first-line treatment, because this allele is associated with reduced response to antidepressants.<sup>42,43</sup> More distressing is the possible association of this allele with increased suicide risk, particularly violent suicide<sup>44</sup> or repeated suicide attempts.<sup>45</sup>

Furthermore, a functional MRI study of patients who were anxious revealed that in individuals with the short allele, administration of citalopram was associated with increased amygdala activity in response to negative stimuli, and reduced activity in response to positive stimuli.<sup>46</sup> This suggests that antidepressant treatment may actually worsen fear response in patients

## Table

## PTSD-specific symptoms

Category	Symptoms
Re-experiencing	Flashbacks, nightmares, frightening thoughts
Avoidance	Staying away from places, events, or objects that are reminders of the traumatic experience; avoiding thoughts or feelings related to the traumatic event
Arousal and reactivity	Being easily startled, feeling tense or on edge, having angry outbursts, and having difficulty sleeping

PTSD: posttraumatic stress disorder  
**Source:** Reference 8

with PTSD. Clearly, additional research is needed to determine if having the *SLC6A4* gene alters clinical outcomes in response to an antidepressant in a patient with PTSD. In the meantime, clinicians should use vigilance and a critical mindset when they administer antidepressants to a patient who has PTSD.

**Catechol-o-methyltransferase (COMT)** is one of the enzymes that degrades catecholamines such as dopamine, epinephrine, and norepinephrine (NE).<sup>47</sup> In humans, COMT protein is encoded by the *COMT* gene. This gene is associated with allelic variants; the best-studied of these is Val158Met. *COMT* Val158Met polymorphism (rs4860) has been linked to deficits in stress response and emotional resilience.<sup>48,49</sup> Val158Met is associated with a 40% reduction in enzyme activity and slower catalysis of catecholamines, resulting in increases in catecholamines levels in the brain, which may increase the risk of developing PTSD.<sup>50</sup> Individuals homozygous for this SNP (Met/Met) are highly susceptible to develop PTSD independently of the severity of the trauma they experienced.<sup>51</sup> The Val158Met polymorphism may be associated with other abnormalities, such as cognitive problems with specific frontal cortical activity, and also with improved antidepressant response (valine homozygotes less responsive than methionine homozygotes).<sup>52</sup> This gene is available on gene testing profiles.

### The role of norepinephrine in PTSD

Perhaps the greatest advance in the understanding of the pathophysiology of PTSD relates to changes in brain NE. The HPA axis is responsible for coordinating the hormonal response to stress. Dysregulation of this axis and increased activity of the central and peripheral noradrenergic systems are usually observed in patients with PTSD.<sup>53</sup> Several monoamine neurotransmitters are important in the regulation and function of the HPA axis. Norepinephrine plays a major role in stress.

The clinical PTSD-specific criteria are all descriptions of excessive noradrenergic tone.<sup>54</sup> For example, hypervigilance and hyperstartle are clearly anticipated as evidence of NE stimulation. Flashbacks, particularly those that might be precipitated by environmental cues, also can be a manifestation of the vigilance induced by NE. Sleep disturbances (insomnia and nightmares) are present; insomnia is reported more often than nightmares.<sup>55</sup> Increased catecholamine levels, particularly NE, are a feature of sleep disturbances associated with middle insomnia. Dreams can be remembered only if you wake up during dreaming. Catecholamines do not change the content of dreams, just recall.<sup>56</sup>

In a study of central noradrenergic tone in patients with PTSD, 6 hourly CSF samples were collected from 11 male combat veterans with PTSD and 8 healthy controls.<sup>57</sup> Participants with PTSD had

### Clinical Point

**The clinical PTSD-specific criteria are all descriptions of excessive noradrenergic tone**

## Clinical Point

One study found that patients with PTSD had significantly higher CSF norepinephrine levels

## Related Resources

- North CS, Hong BA, Downs DL. PTSD: a systematic approach to diagnosis and treatment. *Current Psychiatry*. 2018;17(4):35-43.
- Zhang Y, Ren R, Sanford LD, et al. The effects of prazosin on sleep disturbances in post-traumatic stress disorder: a systematic review and meta-analysis. *Sleep Med*. 2019; 67:225-231.

### Drug Brand Names

Aripiprazole • Abilify	Prazosin • Minipress
Citalopram • Celexa	Quetiapine • Seroquel
Paroxetine • Paxil	Sertraline • Zoloft

significantly higher CSF NE concentrations ( $0.55 \pm 0.17$  pmol/ml vs  $0.39 \pm 0.16$  pmol/mL in the PTSD and control groups, respectively;  $F = 4.49$ ,  $P < .05$ ).<sup>57</sup> Overall PTSD symptoms correlated significantly with CSF NE levels ( $r = 0.82$ ,  $P < .005$ ), and PTSD-specific symptoms such as avoidance ( $r = 0.79$ ,  $P = .004$ ), intrusive thoughts ( $r = 0.57$ ,  $P = .07$ ) and hyperarousal ( $r = 0.54$ ,  $P = .09$ ) were also related.<sup>57</sup> This relationship is unique; patients with PTSD with predominant depressive symptoms do not have elevated plasma NE levels.<sup>58</sup>

In the human brain, there are 3 main groups of NE receptors: alpha-1 receptors, alpha-2 receptors, and beta receptors.<sup>59</sup> Alpha-1 receptors (alpha-1A, alpha-1B, and alpha-1D) are postsynaptic and mediate increase in inositol trisphosphate ( $IP_3$ ) and intracellular calcium ( $Ca^{2+}$ ). Alpha-2 receptors (alpha-2A, alpha-2B, alpha-2C) in the CNS are presynaptic autoreceptors and serve to reduce NE release. Beta receptors (beta-1, beta-2, beta-3) inhibit cyclic

adenosine monophosphate (cAMP) production.<sup>59</sup> The effects of inhibition of alpha or beta receptors are different. Inhibition of beta receptors is associated with depressive symptoms and depressive syndrome, inhibition of peripheral beta receptors is associated with reductions in anxiety (generally reduction of pulse, sweating, tremor),<sup>60</sup> and inhibition of central alpha-1 receptors is associated with reduced PTSD symptoms.<sup>61</sup>

## Choice of agents for PTSD-specific symptoms

As outlined in the *Table*<sup>8</sup> (page 35), PTSD is characterized by 3 types of symptoms that are specific for PTSD. Trauma-focused psychotherapy<sup>62,63</sup> and selective serotonin reuptake inhibitors (SSRIs)<sup>64</sup> are considered first-line therapy for PTSD. Only sertraline and paroxetine are FDA-approved for treating PTSD. However, the effect size for SSRIs is quite small; improvement is only 23% to 30% greater than placebo.<sup>64,65</sup> Furthermore, studies have shown that these medications have little effect on insomnia, hyperarousal, or other PTSD-specific symptoms.<sup>66,67</sup> Studies examining military veterans with PTSD have found that these patients tend to have little or no response to antidepressants.<sup>68,69</sup>

Serotonin transporter promoter region gene short-type variants, which possibly increase an individual's predisposition to developing PTSD, may explain the abundance of depressive symptoms in this condition and the subdued response to antidepressants. Specifically, an anticipated preponderance of these alleles may

## Bottom Line

Understanding the mechanisms of the pathophysiology of posttraumatic stress disorder (PTSD) may allow clinicians to “jump ahead” of clinical studies and FDA indications. Clinicians may reasonably use alpha-1 antagonists (eg, prazosin, quetiapine) for general clinical improvement of patients with PTSD, particularly for PTSD-specific symptoms. Using antihistamines to reduce anxiety (especially in patients who have the *COMT* Val158Met polymorphism) may also be reasonable.

be associated with poorer outcomes. Non-SSRI treatments, such as low-dose aripiprazole, may be alternatives,<sup>70</sup> but these approaches have not been adequately developed.

On the other hand, animal models support antagonism of the postsynaptic alpha-1 adrenergic receptor of the CNS as a target for PTSD treatment.<sup>71</sup> Although prazosin is not currently FDA-approved for treating PTSD, in placebo-controlled studies, nightmares and PTSD total symptoms improved with prazosin, and evidence suggests that it should be used 2 or 3 times a day for all PTSD symptoms.<sup>61</sup> Prazosin may be helpful for treating sleep problems commonly experienced by people with PTSD. Blockade of histamine will also improve sleep disturbance and reduce nightmares, but it may not be as effective as prazosin.<sup>72</sup>

Quetiapine might be another non-SSRI option for treating patients with PTSD. It is an antagonist with high affinity to the histamine-1 receptor at low doses. Norquetiapine is an alpha-2 antagonist that increases brain NE levels. Both quetiapine and norquetiapine are alpha-1 antagonists. There is no beta blockade and no SSRI effect, but some 5HT<sub>2A</sub> blockade, which may be anxiolytic. Compared with placebo, an average quetiapine dose of 258 mg/d resulted in significantly greater reductions in Clinician-Administered PTSD Scale total score, re-experiencing score, and hyperarousal score.<sup>73</sup>

Unfortunately, none of the non-SSRI options have been adequately evaluated. For now, clinicians need to continue to use SSRIs, and researchers need to continue to explore mechanism-guided alternatives.

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## Clinical Point

### Animal models support antagonism of the postsynaptic alpha-1 adrenergic receptor of the CNS as a target for PTSD treatment

## Clinical Point

## Quetiapine resulted in significant reductions in Clinician-Administered PTSD Scale scores

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