Mr. S, 64, has a history of post-traumatic stress disorder (PTSD), which has been well controlled for the past 15 years with cognitive-processing therapy and fluoxetine, 40 mg/d. However, over the past 6 weeks, Mr. S has experienced increased hypervigilance, nightmares, and flashbacks. He states that his primary care provider recommended an adjustment in pharmacotherapy to address this exacerbation of symptoms. Previous medication trials include sertraline, 200 mg/d, discontinued due to lack of perceived efficacy, and venlafaxine, 150 mg/d, discontinued due to increased blood pressure.

Mr. S’s medical history includes hypertension, dyslipidemia, and myocardial infarction (MI) 5 years ago. His family history includes sudden cardiac death (mother and father) and major depressive disorder (sister). His blood pressure is currently uncontrolled on lisinopril, 5 mg/d, and metoprolol succinate, 50 mg/d. Today, serial blood pressure readings measured approximately 180/90 mm Hg, with a pulse 50-60 beats per minute.

What is the next step in treating Mr. S’s hypertension and PTSD symptoms? Is there any evidence to support concomitant therapy?

PTSD is characterized by emotional and behavioral symptoms following exposure to a traumatic event. Its 12-month prevalence in the United States is estimated at 3.5%. Diagnostic criteria necessitate the presence of intrusive symptoms, persistent effortful avoidance of distressing trauma-related stimuli, negative cognitions or mood, and alterations in arousal and reactivity. PTSD negatively impacts social and occupational functioning.

Cardiovascular disease (CVD) comprises a number of conditions, including coronary artery disease, cerebrovascular disease, congestive heart failure, and venous thromboembolism. CVD accounted for more than 17 million deaths worldwide in 2012, which is more than any other cause.

Studies have revealed a correlation between the presence of psychosocial factors, such as depression and anxiety, and the occurrence of cardiovascular events.
The mechanism appears to consist of a behavioral component (eg, poor diet, tobacco use) and a direct pathophysiologic component (eg, excessive sympathetic nervous system activation) (Table 1). Management of concomitant PTSD and CVD presents a challenge to clinicians. This article summarizes the evidence for the use of CVD medications in treating PTSD (Table 2, page 40) and how to apply these principles in patient care (Table 3, page 41).

### ACEIs, ARBs, beta blockers, and calcium channel blockers

Angiotensin-converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) inhibit the renin-angiotensin system: ACEIs prevent formation of angiotensin II, a potent vasoconstrictor, and ARBs prevent interaction between angiotensin II and its receptor. In one study, patients were recruited from a large public hospital serving primarily a highly traumatized, low-income population. Patients taking an ACEI or ARB who had experienced at least 1 traumatic event exhibited significantly decreased hyperarousal symptoms and decreased intrusive thoughts on the PTSD Symptom Scale and Clinician Administered PTSD Scale. Other studies have reported that blockade of angiotensin II AT1 receptors may result in decreased stress, anxiety, and inflammation. Evidence supports the use of the centrally acting, beta-adrenergic antagonist propranolol for decreasing the physiologic reactivity to acute trauma. Emotional arousal enhances the consolidation of emotional experiences into long-term memories via the adrenal stress hormones epinephrine and cortisol. The amygdala mediates these stress hormones and releases norepinephrine, which subsequently activates noradrenergic receptors essential for memory enhancement. Several studies have reported that patients who received propranolol within several hours of a traumatic event experienced fewer physiologic signs of PTSD at follow-up 1 month later. Moreover, researchers have hypothesized that chronic treatment with propranolol may be effective in decreasing hyperarousal symptoms in patients with chronic PTSD by reducing tonically elevated norepinephrine signaling.

Chronic elevation of noradrenergic activity may induce lipoprotein lipase and suppress low-density lipoprotein (LDL) receptor activity, which in turn elevates serum cholesterol levels. The results of one study suggested that verapamil, a non-dihydropyridine calcium channel blocker, significantly improves serum cholesterol levels in patients with PTSD by increasing LDL receptor activity and decreasing norepinephrine release.

### Table 1

**Increased CVD risk factors among veterans with PTSD**

<table>
<thead>
<tr>
<th>Risk factor</th>
<th>Odds ratio, male</th>
<th>Odds ratio, female</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypertension</td>
<td>2.88</td>
<td>2.99</td>
</tr>
<tr>
<td>Dyslipidemia</td>
<td>2.70</td>
<td>2.68</td>
</tr>
<tr>
<td>Type 2 diabetes mellitus</td>
<td>2.57</td>
<td>2.86</td>
</tr>
<tr>
<td>Obesity</td>
<td>2.35</td>
<td>3.01</td>
</tr>
<tr>
<td>Tobacco use</td>
<td>3.63</td>
<td>3.58</td>
</tr>
</tbody>
</table>

CVD: cardiovascular disease; PTSD: posttraumatic stress disorder

*Compared with veterans with no mental health diagnosis or with a mental health diagnosis other than PTSD

**Source:** Reference 3

continued
Alpha-1 and alpha-2 antagonists

Alpha-1 antagonists relax vascular smooth muscle by blocking norepinephrine stimulation at postsynaptic α-1-adrenergic receptors. They frequently are prescribed for hypertension and benign prostatic hyper trophy. One α-1 antagonist in particular, prazosin, appears especially useful in treating sleep disturbances, which occur in up to 90% of patients with PTSD.17 Because of its relatively greater lipophilicity, prazosin crosses the blood–brain barrier and acts centrally to reduce the fight-or-flight and hyperarousal reactions related to nightmares caused by PTSD.18 Common adverse effects include dizziness and orthostatic hypotension. These usually can be mitigated with titration to effective dose. In a study of active-duty soldiers who returned from Iraq and Afghanistan, Raskind et al8 found that prazosin doses up to 25 mg/d in men and 12 mg/d in women were tolerated with weekly adjustments and blood pressure monitoring.

Other α-1 antagonists have shown efficacy in a limited number of trials and may be considered second-line treatment of PTSD hyperarousal symptoms. Doxazosin has a longer half-life compared with prazosin (22 hours vs 3 hours) and may be useful in treating daytime hyperarousal with once-daily dosing. However, its hydrophilicity prevents it from crossing the blood–brain barrier to the same degree as prazosin.19 Terazosin also has a longer half-life (12 hours) and reaches peak plasma concentration in 1 hour. It undergoes minimal first-pass metabolism, leaving almost the entire circulating dose in the parent form, but clinical data are limited to only a small case report.10

Alpha-2 agonists inhibit sympathetic outflow in the CNS, which ultimately relaxes vascular smooth muscle like α-1 antago-
Clinical Point

Case reports and open-label trials have suggested that guanfacine may reduce trauma-induced nightmares in pediatric patients.
Clinical Point

TCAs should be avoided in patients with CVD because they may exacerbate cardiac conduction abnormalities.

References


Related Resource


Drug Brand Names


